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CARBOHYDRATE METABOLISM IN HYPERTHYROIDISM*

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I have attempted in this study to investigate the blood sugar and glycosuria in cases of hyperthyroidism. When this investigation was started it was my intention to study the blood sugar and glycosuria in every type of disease of the thyroid gland, so that this series includes about ten cases of colloid goiter without hyperthyroidism. The cases which were studied were not consecutive but were chosen because they showed either glycosuria or hyperglycemia two and one-half or more hours after a meal.

The carbohydrate metabolism has been determined in each case by glucose tolerance tests made uniformly by the following method: One hundred grams of glucose in 250 cc. of ice-cold water plus the juice of one lemon is given by mouth in the morning before any food is taken. Blood is taken for sugar estimations before the glucose is administered and at successive intervals of one-half, one, two, three and four hours thereafter.

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TABLE I

DATA IN 92 CASES OF HYPERTHYROIDISM AND SIMPLE GOITER IN WHICH GLUCOSE TOLERANCE TESTS WERE MADE

Number	Date When Seen	Glycosuria First Discovered	Fasting Blood Sugar	Sex	Age	Weight			Thyroidectomy	Remarks
						Weight	% Overweight	% Underweight		
100731	3-15-21	Negative	165	F	55	....	....	....	5-22-20	
102977	5-24-21	1- 9-22	256	F	40	210	65	....	9-28-20	
105096	8- 2-21	8- 3-21	112	M	64	....	....	....	.....	
109856	1-24-22	1920	87	M	34	190	28	....	12- 1-26	Note decreased tolerance when hyperthyroidism developed.
111876	4- 7-22	1920	129	M	55	....	....	....	.....	
116219	9- 1-22	9- 1-22	85	M	43	....	....	....	8-15-23	
120165	1-16-23	9-10-22	187	F	52	140	10	....	.....	
122866	4-17-23	4-17-23	141 (3)	F	50	....	....	30	.....	
123327	5- 2-23	4-30-26	77	F	49	215	53	....	5- 4-23	Thyroidectomy 1911. Gained 50 lbs., 3 mos.
127104	9-18-23	9- ?-23	76	M	49	....	....	....	.....	
131355	12-14-23	3- ?-23	110	M	38	140	....	....	12-18-23	Normal B. S. 1 year later.
133039	2- 8-24	2- 9-24	76	M	39	145	6	....	.....	
134132	3-10-24	Negative	145	F	72	....	....	....	3-13-24	
145891	1-12-25	1-12-25	...	F	40	175	30	....	.....	
147421	2-17-25	Negative	216	F	60	....	....	....	.....	
149341	4- 2-25	1- 2-25	280	F	20	92	....	41	.....	
152201	6- 9-25	1923	275 (3)	F	52	....	....	....	.....	
152737	6-22-25	Negative	95	F	32	....	....	....	8-18-25	4-15-26 glycos. after influenza.
155420	8-20-25	3- ?-25	...	F	57	....	....	....	9- 3-25	
155744	8-26-25	Negative	141 (2)	M	30	131	....	....	.....	
157541	10- 5-25	10- 6-25	98	F	45	111	....	26	10-15-25	
158002	10-17-25	7- ?-25	114	M	43	140	....	....	9-21-26	
158046	10-23-25	Negative	136	F	54	....	....	....	10-28-25	Lost 40 lbs. in 6 mos.
158782	11- 5-25	1922	55	M	47	....	....	....	.....	Quite emaciated.
149049	11-11-25	11-11-25	95	F	50	....	....	....	4- 2-26	Lost 15 lbs.
159737	12- 2-25	Negative	98	F	42	....	....	....	.....	Lost 50 lbs.
159681	12-10-25	1923	226 (4)	F	46	....	....	....	12-14-25	
160342	12-15-25	1924	219	F	60	154	....	....	12-22-25	
160731	12-29-25	12-29-25	94 (3¾)	F	32	....	....	....	1-19-26	Lost 45 lbs.
162170	2- 4-26	2- 4-26	186	M	26	....	....	....	.....	
164227	3-23-26	Negative	101 (1)	F	28	220	59	....	12- 8-26	

TABLE I—Continued

Number	Date When Seen	Glycosuria First Discovered	Fasting Blood Sugar	Sex	Age	Weight			Thyroidectomy	Remarks
						Weight	% Overweight	% Underweight		
165508	4–19–26	4–19–26	179 (3¼)	M	29	128	....	....	.....	
165767	4–26–26	Negative	101 (4½)	F	20	174	29	....	5– 8–26	Lipodystrophy and hyperthyroidism.
165752	4–26–26	Negative	102	F	34	160	....	....	4–28–26	Thyroidectomy 1919. Acromegaly.
167566	6– 1–26	Negative	97 (4)	F	48	296	55	....	.....	Thyroidectomy in 1916.
167620	6– 2–26	6– 2–26	134 (2)	F	58	115	....	33	11– 9–26	Lost 33 lbs.
167654	6– 2–26	6–28–26	85	F	49	95	....	21	11–10–26	
168150	6–12–26	Negative	89 (2½)	F	27	142	25	....	.....	
168491	6–18–26	Negative	111	F	10	55	....	10	2–14–27	
168510	6–18–26	Negative	66	M	29	140	....	....	.....	
169053	6–29–26	Negative	68	F	17	104	....	2	7–16–26	Thirst, frequency, nervousness.
170000	7–19–26	1– ?–26	93 (3)	M	54	147	....	25	.....	Thyroidectomy 1917.
170904	8– 6–26	Negative	96	F	39	....	....	....	8–24–26	Lost 50 lbs. in 6 mos.
171841	8–27–26	1–24–27	192	F	45	98	....	20	9– 3–26	
171949	8–30–26	Negative	105 (6)	F	33	113	....	10	.....	
172110	9– 1–26	Coma 5–25	187 (4)	M	36	135	....	17	9–16–26	Lost 17 lbs.
172219	9– 3–26	9– 3–26	76	M	51	102	....	61	.....	Lost 35 lbs.
172346	9– 7–26	9– ?–25	102F	M	56	178	....	....	.....	
172311	9– 7–26	9– 7–26	72	M	35	140	....	21	12– 1–26	Marked nocturia.
172566	9–10–26	Negative	122	M	50	115	....	27	8–20–26	
172569	9–10–26	9–10–26	88	F	51	118	....	11	9–25–26	Loss of weight.
172758	9–14–26	Negative	146 (2½)	F	48	167	....	....	9–28–26	
173493	9–29–26	9–28–26	270 (2)	F	55	130	....	9	.....	
173894	10– 7–26	10–25–26	92 (5½)	F	51	99	....	25	11– 4–26	
174309	10–18–26	7–18–26	173 (1½)	F	56	81	....	47	11– 4–26	
174593	10–22–26	Negative	150 (3¼)	F	61	110	....	18	.....	Hyperthyroidism developed after use of iodized salt.
175328	11– 8–26	Negative	139 (4)	M	60	111	....	29	3–17–27	
175632	11–15–26	Negative	73	M	25	151	....	....	11–30–26	
175685	11–15–26	10–13–26	97	M	62	160	....	34	.....	
175766	11–17–26	11–17–26	194 (3½)	F	56	122	....	....	11–30–26	
175849	11–18–26	11–18–26	119	F	49	140	....	....	3–14–27	
176197	11–29–26	Negative	125 (3½)	F	37	151	....	....	12–18–26	

TABLE I—Concluded

Number	Date When Seen	Glycosuria First Discovered	Fasting Blood Sugar	Sex	Age	Weight			Thyroidectomy	Remarks
						Weight	% Overweight	% Underweight		
176410	12- 1-26	12- 8-26	169	F	59	132	....	10	12-16-26	
176905	12-15-26	.....	143	F	30	89	....	51	1- 5-27	Died 1-6-27.
178015	1-15-27	Negative	99	F	19	105	....	10	2- 2-27	
178032	1-17-27	Negative	125	F	35	112	....	10	.....	
178213	1-20-27	Negative	152	F	69	176	30	....	1-28-27	
178234	1-20-27	1-20-27	81	M	34	145	....	5	1-24-27	
178470	1-27-27	2- 9-27	155	F	46	116	....	10	2- 8-27	
178688	2- 1-27	2- 2-27	400	F	45	150	5	....	12- 1-22	
178736	2- 2-27	2- 2-27	130	F	48	95	....	26	.....	
178992	2- 8-27	2- 8-27	161	F	39	153	16	....	2-18-27	
179177	2-12-27	Negative	110	M	13	101	5	....	.....	
179222	2-14-27	2-14-27	167	F	59	167	34	....	.....	
179214	2-14-27	2-14-27	116	F	39	116	....	22	2-24-27	
179260	2-15-27	Negative	163	F	53	137	10	....	.....	
179357	2-16-27	2-16-27	272	F	56	94	....	20	.....	
179934	3- 2-27	3- 2-27	255	F	58	124	....	....	.....	
179977	3- 3-27	1917	179	M	59	....	....	30	3-21-27	
180132	3- 7-27	Negative	97	F	23	185	37	....	3-22-27	
180192	3-10-27	3-22-27	98	F	31	....	....	....	3-21-27	
180296	3-11-27	Negative	97	F	10	53	....	10	.....	
180388	3-13-27	3-14-27	134	F	40	....	....	....	3-25-27	
180565	3-17-27	Negative	153	F	43	123	....	10	.....	
180592	3-18-27	Negative	140	F	26	117	....	12	.....	
180714	3-21-27	Negative	161	M	51	97	....	34	.....	
180739	3-22-27	Negative	178	F	46	117	....	....	4- 4-27	
180779	3-22-27	Negative	114	M	29	153	....	....	.....	
180780	3-22-27	Negative	98	M	48	330	82	....	3-30-27	
181458	4- 6-27	Negative	97	M	25	132	....	16	.....	
181530	4- 7-27	4- 7-27	147	F	48	84	....	45	.....	
181509	4- 7-27	Negative	117	F	51	86	....	42	4-15-27	

Two hundred cubic centimeters of ice-cold water is given hourly by mouth. Urine is taken at the same intervals—with the exception of one-half hour after the ingestion of the glucose—for both qualitative and quantitative examinations for sugar. This routine has been identical for all patients in this group with the exception of two children 10 and 12 years of age, respectively, who received 75 gm. of glucose. The blood sugar estimations have been made by the Myer-Benedict method, the blood being oxalated, and tested immediately in most cases, although in a few instances it was kept on ice for two hours before it was tested. Basal metabolism estimations have been made whenever this was feasible.

TABLE II

SEX AND AGE INCIDENCE IN CASES OF HYPERTHYROIDISM IN WHICH GLUCOSE TOLERANCE TESTS WERE MADE

Decades	1	2	3	4	5	6	7	8	Total No. Tests
Male	..	1	8	9	6	7	2	..	33
Female	2	4	7	14	16	20	3	1	67

TABLE III

PERCENTAGE OF OVERWEIGHT AND UNDERWEIGHT IN CASES OF HYPERTHYROIDISM IN WHICH GLUCOSE TOLERANCE TESTS WERE MADE

Percent	5	10	15	20	25	30	35	40	45	50	55	60	65	85	Total
Over weight	3	2	..	1	1	5	1	1	..	..	2	1	1	1	19
Under weight	2	9	2	5	5	6	3	..	3	1	1	..	1	..	38

TABLE IV

THE AMOUNT OF SUGAR EXCRETED DURING GLUCOSE TOLERANCE TESTS

Sugar, gram	1	2	3	4	5	5–10	10–20	20–30	30–40	40–50
Number of cases	24	17	5	4	6	13	7	1	2	2

In Tables I-IV are given the pertinent data in the 92 cases in the series here presented. One hundred glucose tolerance tests have been made in this series, as in several cases the test was repeated. The ages range from 10 years to 72 years. Either glycosuria or hyperglycemia was present in most of these

cases, this finding leading to the glucose tolerance test in order to determine the degree of the carbohydrate derangement. In such a study as this a large number of basic observations must be made if one is to secure sufficient follow-up data from which to draw conclusions. As these patients come from all over the United States, in only a small group can it be hoped that sufficient data will be secured for a further study.

Nineteen of the patients were overweight and 38 were underweight. The tendency in cases of hyperthyroidism is to lose weight, this being probably due to the increased metabolism which makes a patient burn up, first, his superfluous fat and, later, his body protein. Some of these patients were markedly emaciated. Those in whom the carbohydrate metabolism is considerably disturbed lose weight because of the imperfect oxidation of the carbohydrate and the consequent loss of sugar through the urine.

Two patients in this series died—a mortality rate of 2.1 per cent. In one of these cases death was due to a postoperative pulmonary collapse; the other case was that of an old woman 72 years of age with very severe hyperthyroidism, who died from collapse the day after operation.

In this series of 92 cases thyroidectomy was performed in 57, or 62 per cent. In a few of these cases—perhaps ten—only ligations have thus far been performed, and the thyroidectomy will be done at a later date. In one case which will be reported in another section of this paper, the symptoms of hyperthyroidism disappeared entirely as the result of insulin treatment alone. In another case, not included in this series, a patient with very severe hyperthyroidism associated with severe diabetes has not responded in the least to large doses of insulin, as far as the symptoms of hyperthyroidism are concerned, though the diabetes is controlled. This patient has been under observation since October, 1925, and there are so many interesting phases about his case that it will be reported later, when the problems which it presents are more nearly solved.

A study of the tolerance tests shows a range of response from the perfectly normal to that which indicates the presence of very severe diabetes. There is no definite line of demarcation between the normal and the diabetic state, and no matter

where one might put the dividing line, the high incidence of diabetes would still be evident.

In this study I have tried to call attention to the fact that there is a disturbance of carbohydrate metabolism in hyperthyroidism, and that this is not a rare finding is evident. I feel that such a disturbance is the result of the great drain on the insulogenic mechanism due to the increased metabolism. Such an increased drain is of no consequence in individuals who have a good reserve in the islands of Langerhans, but it is of great consequence in cases in which this insulogenic reserve is small. These cases, and these cases only, I think, show hyperglycemia. They may show glycosuria or they may not, since this depends on the height of the renal threshold in the individual case as well as upon the corresponding degree of hyperglycemia.

The permeability of the renal filter seems to be increased in some cases. Whether it is increased in all cases I cannot say, since, to determine this, would necessitate definite studies of the condition of these individuals before hyperthyroidism developed in order to compare the renal threshold at that time

TABLE V

PRESENCE AND ABSENCE OF GLYCOSURIA DURING GLUCOSE TOLERANCE TESTS

	Before Ingestion of Glucose	After Ingestion of Glucose			
		1 Hour	2 Hours	3 Hours	4 Hours
Glycosuria present.....	19	75	81	58	38
Glycosuria absent.....	81	25	19	42	62

Glycosuria present at some time during glucose tolerance test in 81 cases.
Glycosuria absent during the entire glucose tolerance test in 19 cases.

with the threshold during the active stage of hyperthyroidism. We know that both in animals and in man thyroidectomy eliminates glycosuria; but it also reduces glycemia, hence this fact proves nothing as far as the renal threshold is concerned.

The glucose tolerance estimations in this series showed fasting glycosuria to be present in 19 tests and absent in 81 tests (see Table V). Glycosuria was present in the majority of cases in the first, second and third hours, and was absent in the ma-

jority of cases in the fourth hour. It was present at some time or other during the test in 81 cases and absent during the entire test in 19. Sixty-six per cent of these cases present an impaired tolerance; only 34 per cent showing a normal curve. This general impairment of glucose tolerance can best be demonstrated by the 100 curves which are given in Figures I to VII.

The amount of sugar excreted varied from one to 50 grams. In most cases (69 per cent) less than 5 grams was excreted: in 85 per cent less than 10 grams was excreted; and in only 15 per cent was more than 10 grams of sugar excreted.

It is obvious that glycosuria in itself alone does not tell us a great deal regarding the status of the carbohydrate metabolism, unless it is marked and unless we know also the blood sugar response to the ingestion of carbohydrate and the level of renal permeability to sugar. The excretion of sugar by a patient with a low threshold is usually of little or no significance.

According to our observations in this series the state of hyperglycemia is not proportional to the severity of the hyperthyroidism. Were hyperglycemia directly due to hyperthyroidism then certainly the degree of hyperglycemia would bear a direct relation to the degree of hyperthyroidism—but this is not the case. In some of the cases which showed the highest hyperglycemia the degree of hyperthyroidism was the mildest. If in some cases mild hyperthyroidism is sufficient to bring about a diabetic state, and in others severe hyperthyroidism leaves the carbohydrate tolerance undisturbed, one naturally asks, "Why?" It seems to me that the evidence points to but one explanation, namely, that in the former group in which diabetes is produced the islands of Langerhans have a small reserve and thus easily become exhausted, hence a diabetic state is easily brought about by any condition which brings a further strain, in this instance the hyperthyroidism being the disturbing influence.

Figures I, II, III, IV, V, VI, VII, following. Charts showing findings in a series of 100 glucose tolerance tests made in cases of hyperthyroidism and simple goiter.

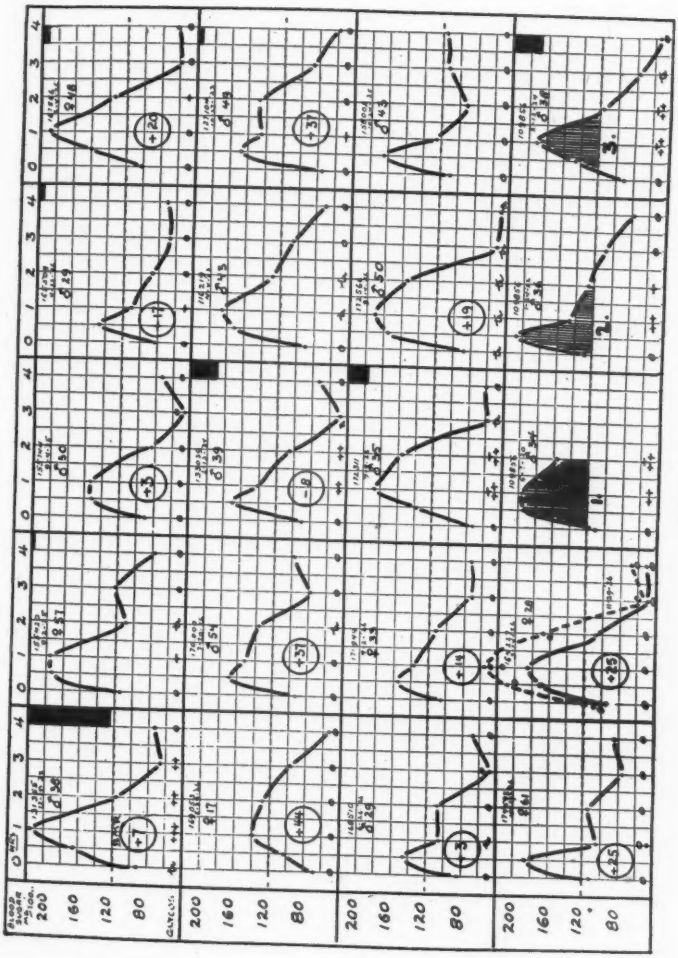

Figure 1

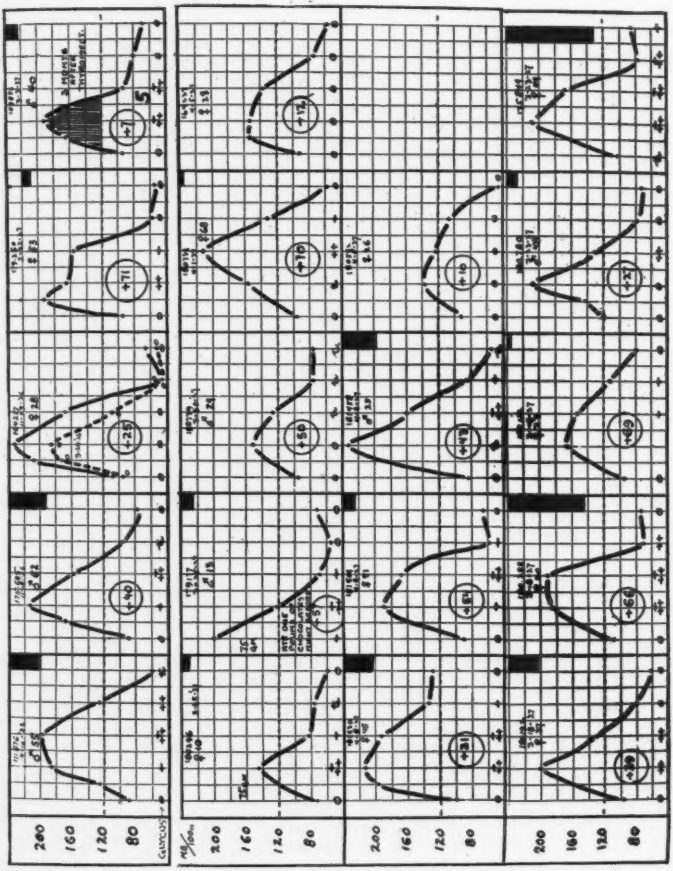

Figure II

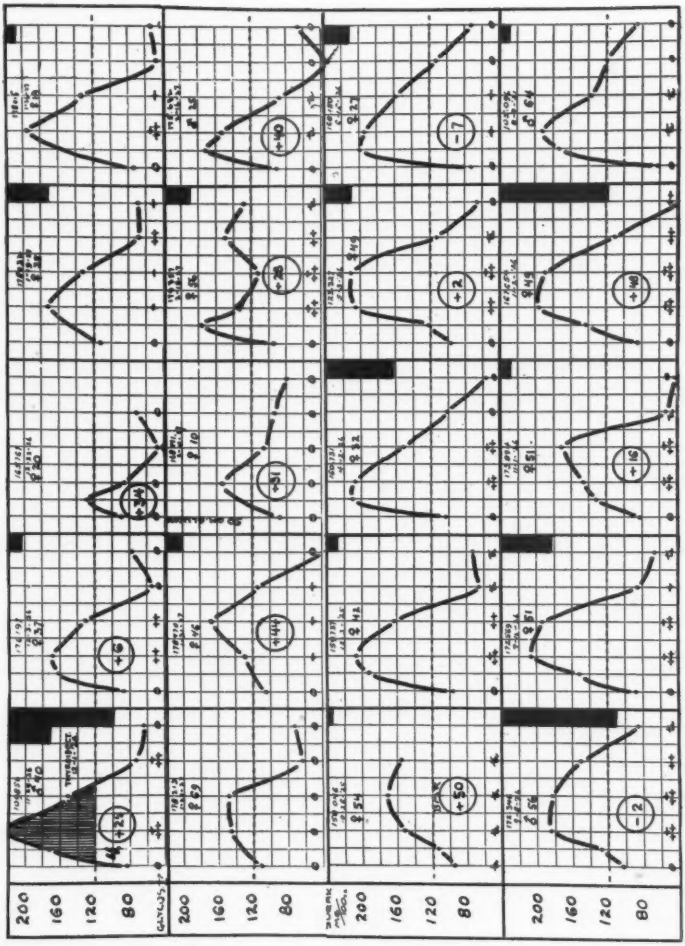

Figure III

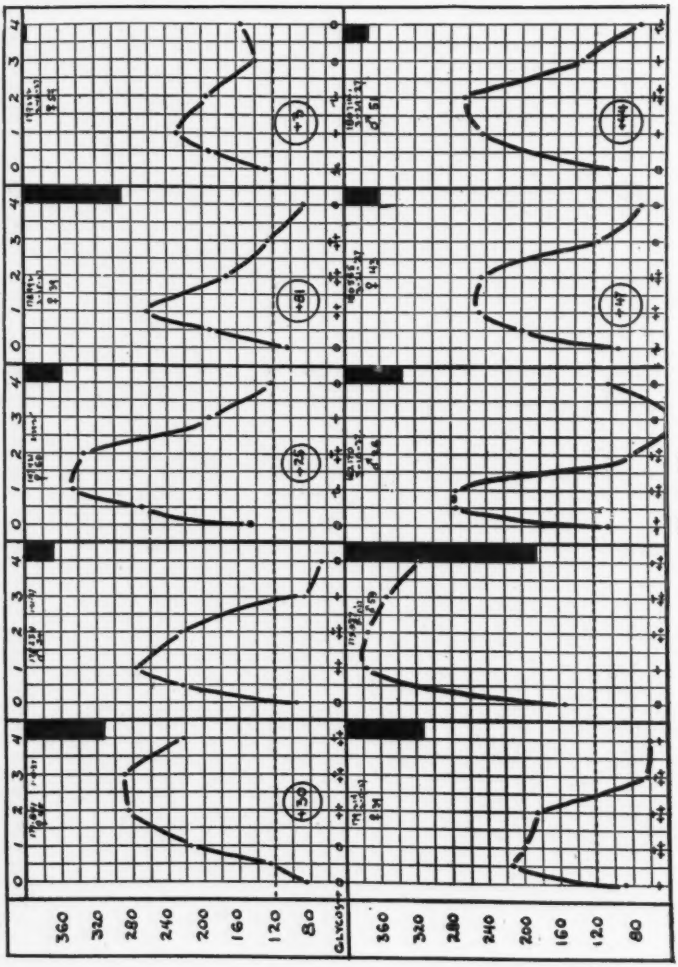

Figure IV

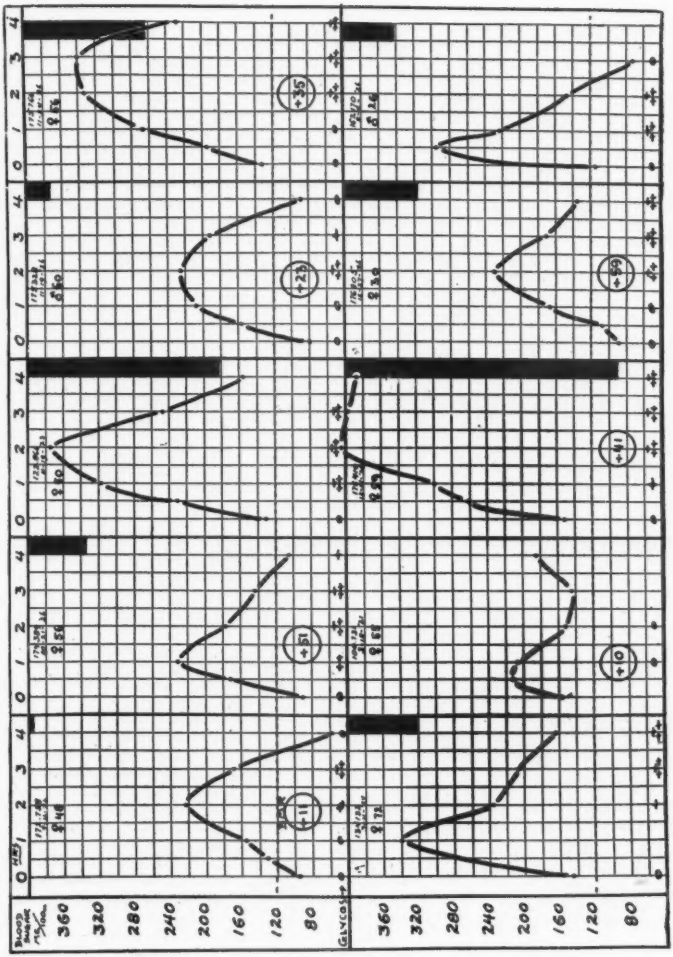
Blood Sugar Mgm.
360
320
280
240
200
160
120
80
Glycosuria
0 1 2 3 4
+11
+51
+10
+41
+23
+99
+35

Figure V

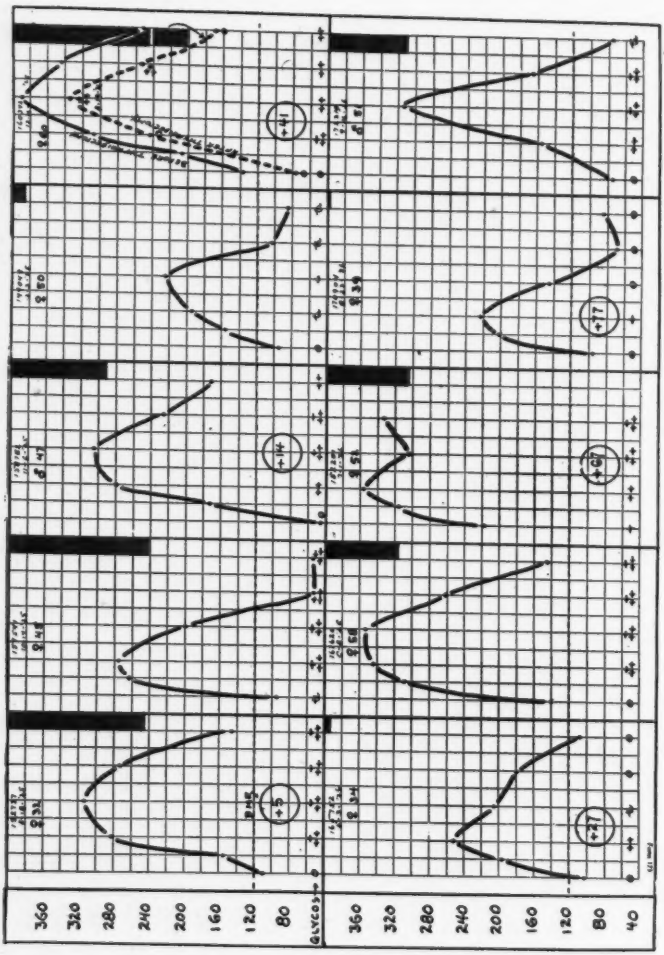

Figure VI

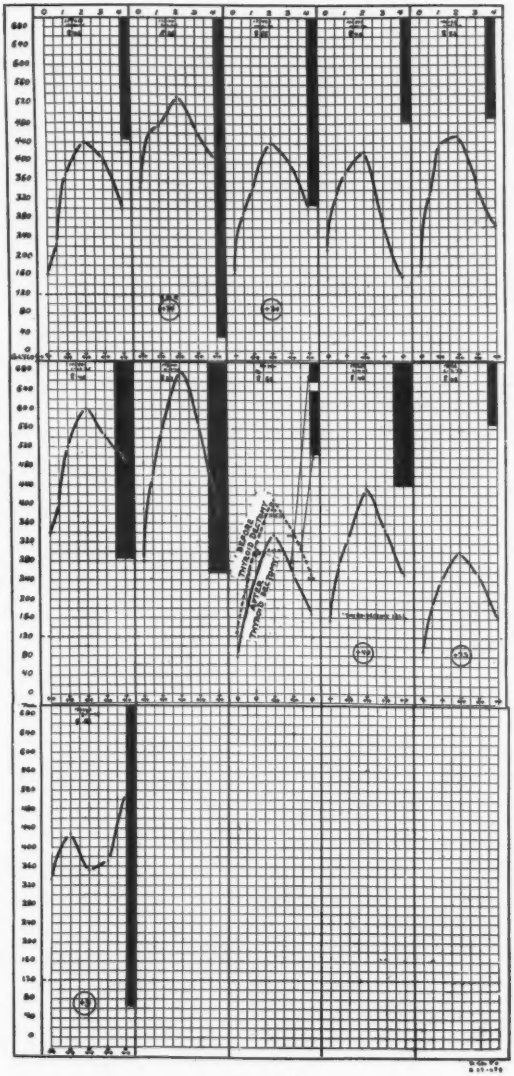

Figure VII

The relationship of the basal metabolic rate to the glucose tolerance in this series is shown in Table VI. It will be noted that in 40 of these cases the curve was diabetic or prediabetic in type and the basal metabolic rates ranged from minus three to plus 90 per cent. The case in which the metabolism was minus three, however, was one of simple goiter, not hyperthyroidism. In the 34 cases in which the glucose tolerance curve was normal in type, the basal metabolic rate varied from minus three per cent to plus 80 per cent.

TABLE VI

THE RELATIONSHIP OF BASAL METABOLIC RATE TO GLUCOSE TOLERANCE IN 66 CASES

	Minus	Plus 1–10	Plus 10–20	Plus 20–30	Plus 30–40	Plus 40–50	Plus 50–60	Plus 60–70	Plus 70–80	Plus 80–90	Total
Number cases....	3	11	8	11	10	10	4	4	4	1	66
Diabetic or prediabetic curve..	2	5	3	7	5	8	3	4	2	1	40 (60.6%)
Normal glucose tolerance curve.	1	6	5	4	5	2	1	0	2	0	26 (39.4%)

On the basis of this study it seems evident that the mild derangements of the carbohydrate tolerance that have been observed in this series of cases are but functional disturbances, which disappear when the offending factor, the thyroid, is eliminated either by operation or by other treatment. As for the effect of insulin on hyperthyroidism, one may reason that it perhaps improves the patient's general metabolic condition, giving him a better chance to store glycogen in the liver and thus to combat acidosis; to store glycogen in the heart muscle and thus to give it a better chance to do its work; and to store glycogen in the muscles and thus to eliminate the instability of the organism in general. There is perhaps nothing specific about its action.

The medical problem involved in these cases is to protect these individuals with a decreased carbohydrate tolerance, rather than to let them drift along unprotected toward diabetes. They should be under surveillance until the physician has satisfied himself that stability has been established. In most of these cases the glycosuria disappears after thyroidectomy and the carbohydrate tolerance is restored to normal; in a few cases

this does not happen. It is important, therefore, to make post-operative examinations to determine whether or not the carbohydrate metabolism has been restored to normal; and when this has not happened, to institute such measures as are indicated. It is much easier to keep a mild diabetic in the mild stage than to treat him successfully after a severe stage has developed.

METHOD FOR THE DETERMINATION OF THE RENAL THRESHOLD

Since the determination of the renal threshold is essential for the correct interpretation of glycosuria, it seems well to describe in some detail our method for its estimation. This can best be done by citing two concrete examples. In Figure VIII are shown the glucose tolerance curves of two cases in this series. The blood sugar curve is represented by the heavy black line, which is intersected by dots that indicate actual blood sugar estimations. At the bottom of each chart the presence of sugar in the urine is indicated by the plus sign, its absence by zero.

An examination of the upper chart in Figure VIII will show that there was no fasting glycosuria when the fasting blood sugar was 130 mgm. per 100 cc. At the end of one hour the urine sugar was three plus and the blood sugar 319 mgm. per 100 cc. It is evident that the renal threshold lies somewhere between these two points; and an approximate figure can be obtained by taking the average of the two blood sugar values, viz., 224. The blood sugar level at the end of the second hour was 375, and at the end of the third hour it was 246 mgm. per 100 cc., and glycosuria was present at the time of each of these estimations. But note that at the end of the fourth hour no glycosuria was present and that the blood sugar had fallen from 246 to 155 mgm. per 100 cc. at the end of the third hour. This must mean that no sugar was excreted while the level was falling from 375 to 246 mgm. per 100 cc., as otherwise some sugar would appear at the end of the fourth hour. The excretion of sugar therefore must have stopped at somewhere about 246 mgm. per 100 cc., which indicates that the original average figure of 224 mgm. per 100 cc. was too low, and that the renal threshold was at or above 246 mgm. per 100 cc.

In the lower curve in Figure VIII it is shown that in this case there was a trace of sugar in the urine when the fasting

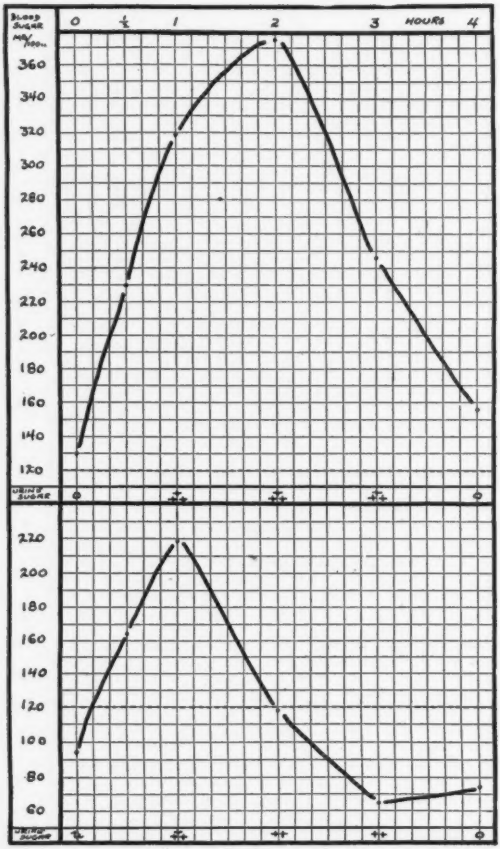

Figure VIII. Charts showing findings in two glucose tolerance tests illustrating the method of estimating the renal threshold (see text).

blood sugar was only 94 mgm. per 100 cc. Does this mean that the threshold lies at or below this blood sugar level? Not at all, because we do not know what was the blood sugar level at the time of the preceding voiding of urine. It is necessary therefore to discard this fasting glycosuria finding and to get what information we may from the following estimates. Between the second and third hours the blood sugar dropped from

118 to 64 mgm. per 100 cc. and there was glycosuria when the latter estimation was made. But although the blood sugar rose between the third and fourth hours from 64 to 74 mgm. per 100 cc., there was no glycosuria at the end of the fourth hour. It is obvious, then, that the glycosuria at the end of the third hour was due to sugar excreted at 118 or below. An average of the third and fifth estimations, therefore, must give us the approximate level of the renal threshold in this case, viz., 96 mgm. per 100 cc.

While this method does not give us absolutely accurate figures, nevertheless it is evident that the findings thereby secured are far more reliable than those obtained by our former procedure of taking the lowest figure at which glycosuria appeared and totally disregarding the preceding blood sugar value.

When glycosuria is present throughout the test no threshold value can be stated; and the same is true when no glycosuria is present at any time during the test.

Table VII shows the findings in 73 glucose tolerance curves in which the level of the renal threshold has been calculated in this manner. It is striking that the threshold was below 120

TABLE VII

RENAL THRESHOLD IN 73 GLUCOSE TOLERANCE TESTS MADE IN CASES OF HYPERTHYROIDISM AND SIMPLE GOITER

Blood sugar mg./100 cc.	60–70	71–80	81–90	91–100	101–110	111–120	121–130	131–140
Number of cases.....	3	3	0	6	3	11	7	4
Blood sugar mg./100 cc.	141–150	151–160	161–170	171–180	181–190	191–200	201–210	211–220
Number of cases.....	4	7	5	4	1	1	3	2
Blood sugar mg./100 cc.	221–230	231–240	241–250	251–260	261–270	271–280	281–290	294
Number of cases.....	4	1	1	1	1	0	0	1

mgm. per 100 cc. in 26 cases, or 35.6 per cent, and that in three cases it was below 70 mgm. per 100 cc. These values on the whole seem lower than would be true of a like series of average clinical cases. Whether the renal permeability is greater in hyperthyroidism I am not prepared to state; I can only offer my findings. Figure IX suggests that this may be a justifiable assumption, as more sugar—5.46 grams—was excreted before operation, when the basal metabolic rate was plus 81 per cent,

than was the case two months after thyroidectomy, when the second tolerance test was made, and only 0.15 gram was excreted; though as the second curve was as high as the first and was more prolonged, one would expect that at least as much if not more sugar would have been excreted. Our findings certainly suggest that there is an increased permeability of the renal filter during active hyperthyroidism.

CRITICAL REVIEW OF THE LITERATURE

I have endeavored to review all the recent reports in the French, German, Czech, English and American literature. At the risk of some repetition this extensive material is critically discussed under the headings which appear pertinent to this general study of the relation of hyperthyroidism to carbohydrate metabolism.

Pathological Changes in the Pancreas Associated with Hyperthyroidism. In 1921 Holst (1) made postmortem studies in four cases in which glycosuria had been associated with exophthalmic goiter. A decrease in the number of the islands of Langerhans and other histological changes in the pancreas were found. There is reason to believe that in Graves's disease the well known anomalies in sugar metabolism are induced by gross anatomical changes of the pancreas in some cases, whereas slight anomalies in the sugar metabolism are only functional in character. In Holst's series seven patients suffering from Graves's disease with alimentary glycosuria were all cured by hemistrumectomy. In three patients with glycosuria the glycosuria disappeared after the operation; in another case diabetes developed and the patient died, although she had previously undergone an operation for exophthalmic goiter. Thyroidectomy, therefore, appears to give good results in mild cases of glycosuria and poor results in severe cases. The glycosuria in experimental diabetes produced by partial extirpation of the pancreas disappears or decreases after thyroidectomy. Normally the thyroid appears to exert an inhibitory action over the pancreas—a point which Allen (2) questions but in support of which Rohdenburg (3) offers an explanation based on pathological evidence. These facts seem to favor the hypothesis that even in the usual cases of non-thyrogenous diabetes there is a therapeutic possibility

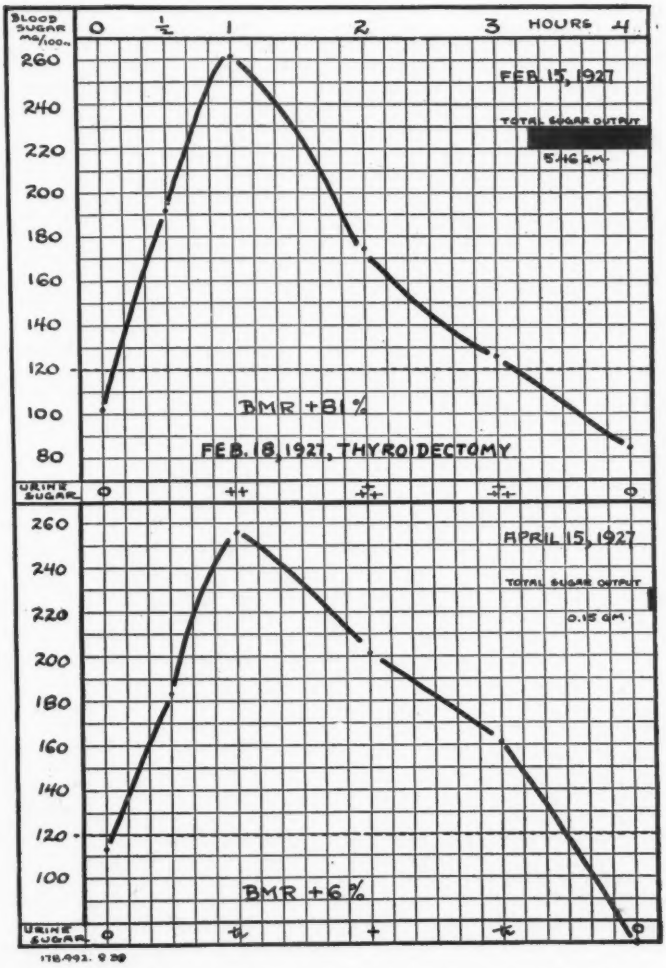

Figure IX. Charts showing findings in two glucose tolerance tests made in the same case, the first before thyroidectomy, the second two months after thyroidectomy. Note that although the hyperglycemia is more protracted in the second test, the sugar output is decreased.

in partial thyroidectomy, not of curing the diabetes but of lessening the hypofunction of the islands of Langerhans.

Rohdenburg (4) reports an interesting case of the spontaneous disappearance of diabetes. The patient was a Russian Jew who, at the age of 30, was refused life insurance on account of glycosuria. Following this she was treated medically but was never sugar-free and she showed the classical symptoms of diabetes during this time. During the following seven years she lost 35 pounds. At the age of 40 a stormy menopause occurred. Three years before her death, with the passing of the menopause, the symptoms of diabetes disappeared, repeated examinations of the urine failed to show sugar and she was able to eat candy without the production of glycosuria. She died in coma of supposedly nephritic origin.

Autopsy revealed hypertrophy of the cardiac muscle with relative valvular insufficiency; marked chronic interstitial nephritis; cystic degeneration of the adrenal glands; fibrotic ovaries; diffuse arteriosclerosis, most marked in the aorta. The thyroid gland showed almost complete destruction of the secreting alveoli and their replacement by connective tissue richly infiltrated with round cells. The head of the pancreas showed marked fibrosis, most of the glandular elements being destroyed and only an occasional island of Langerhans persisting. In the body of the pancreas there was a marked hypertrophy of the islands of Langerhans, most of these being three or four times their usual size. The tail of the pancreas showed no change. These findings in the thyroid and pancreas, in the light of the clinical history, are extremely significant.

The author says that he has seen a similar hypertrophy of the islands of Langerhans in a case of carcinoma of the head of the pancreas associated with Addison's disease, in which both of the adrenal glands had been completely destroyed by tuberculosis. In this case the hypertrophy was chiefly in the body of the pancreas.

Marinesco and Parhon (5) state that removal of the pancreas is followed by signs of over-function of the thyroid gland and that removal of the thyroid is followed by hypertrophy of the islands of Langerhans. Similar changes in the islands have also been reported by Falta (6) and by Lorand (7). Accord-

ing to Allen (2) the observations of these authors await further confirmation.

Garrod (8) refers to a few cases in which exophthalmic goiter was associated with atrophy or other lesions of the pancreas.

The Relation of the Thyroid Gland to Blood Sugar and Glycosuria. Many investigators offer observations on the relationship of hyperthyroidism to blood sugar.

Lüttichau (9) found that athyroidism in animals causes a slight diminution of the blood sugar. Hyperthyroidism produced by thyroid extract, on the other hand, causes a relative hyperglycemia.

Lund and Richardson (10) made blood sugar estimations before and after operations on the thyroid in 29 cases. They found that in patients with hyperthyroidism the blood sugar rose after operation, this rise being similar in every way to that occurring in the other patients. Hypoglycemia did not occur in any case.

Massa (11) found that both in rabbits and in man the blood sugar rose after the application of diathermy to the thyroid region. In exophthalmic goiter this procedure caused a rise which the author explains as probably due to different (sympathicotonic and vagotonic) types of the disease.

Rosenberg (12) studied the glucose tolerance by administering 100 grams of dextrose dissolved in 300 cc. of caffeinless coffee substitute, two hours after breakfast. He found that in cases of Graves's disease the glucose tolerance curves were not regular, being normal in several cases, while in others they resembled a diabetic curve. He thinks that the alterations in the curves do not run parallel to the gravity of the clinical symptoms of hyperthyroidism. Sugar excretion also seemed to be increased in Graves's disease.

Gardiner-Hill *et al.* (13) state that in exophthalmic goiter the blood sugar curves tend to be high and prolonged and that glycosuria is usually present. On the other hand, in 15 well marked cases of myxedema the blood sugar curves were higher and more prolonged than in normal persons. Glycosuria was rarely present. These authors suggest that in myxedema the renal threshold is raised.

Marks (14) noted a secondary hyperglycemia following the

injection of glucose or of small doses of insulin into thyroid-fed rabbits whose livers contained glycogen, but when the liver glycogen was depleted a small dose of insulin or an injection of glucose produced a fatal hypoglycemia.

Waldorp and Trelles (15) found a high degree of glycemia in nine of 19 patients with thyroid disease associated with a high basal metabolism.

San Martin (16) states that the thyroid gland has a special influence on the carbohydrate metabolism and that hyperthyroidism is frequently accompanied by hyperglycemia and even by glycosuria. In hypothyroidism, myxedema and cretinism, on the other hand, the tolerance for carbohydrate is greatly increased. Following the extirpation of the thyroid, the parathyroids being left intact, glycosuria, according to the author, never occurs even after the ingestion of large quantities of sugar. The author has observed two classes of diabetic patients with impaired thyroids: those in whom the diabetes antedated the manifestations of hyperthyroidism and those in whom the signs of Basedow's disease appeared before those of diabetes. He concludes that hyperthyroidism plays a fundamental etiologic rôle in the disturbance of endocrine equilibrium which constitutes the diabetic syndrome.

Experimental work on the effect of thyroxin on the blood sugar is reported by Bodansky (17), who administered thyroxin subcutaneously to sheep and noted a subsequent rise of blood sugar. Small and consistent but temporary increases in the blood sugar were observed soon after single injections. When thyroxin was administered every other day larger increases were observed after variable latent periods. The blood sugar did not stay at a uniformly high level, but wide fluctuations were observed. In thyroidectomized sheep the average blood sugar level was raised only during the first weeks of treatment with thyroxin, when the animals were on an adequate diet and when the blood sugar was taken after a morning in the pasture. During this period the fasting blood sugar would probably have been raised by thyroxin at the expense of the store of glycogen present in the liver at the beginning of the experiment. The fasting blood sugar in the cretin sheep, the glycogen reserve of which had presumably been partly depleted by three months treatment with thyroxin, was about 50 mgm. per 100 cc., a value

similar to that found in untreated cretins. Increased doses of thyroxin produced fluctuations of the blood sugar, the range being between 40 and 60 mgm. per 100 cc., a low range even for a cretin. The "fasting" blood sugar of normal sheep was raised by thyroxin, presumably at the expense of the glycogen store.

Hancher *et al.* (18) administered orally to 32 dogs a glycerol extract of hashed thyroid glands of pigs and produced a marked and sustained rise in the blood sugar. This effect was

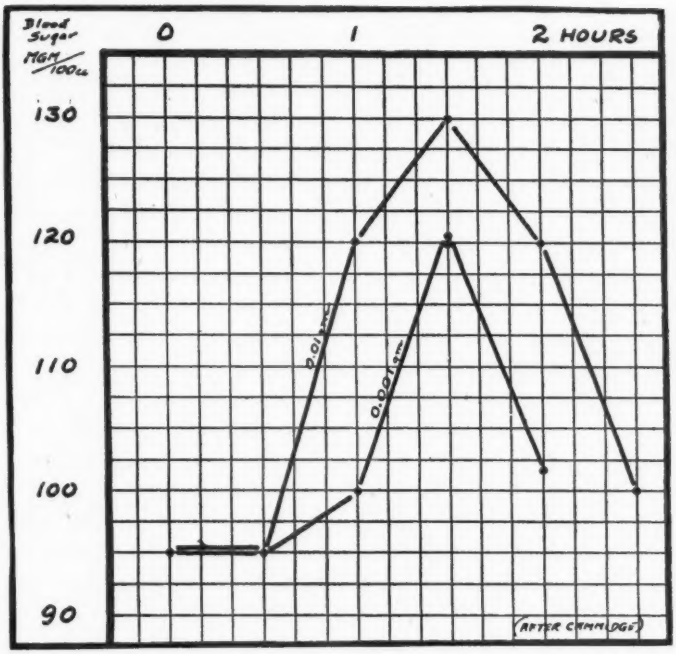

Figure X. Chart showing the rise of blood sugar in a rabbit following the administration of thyroid extract in varying doses. (Plotted from data reported by Cammidge.)

not produced when any of four commonly used commercial preparations of the thyroid gland were administered; one of these, in fact, caused an immediate and distinct decrease in the blood sugar.

Geyelin (19) reports cases of myxedema which showed a

distinct hypoglycemia with blood sugar values as low as 53 and 68 mgm. per 100 cc. Janney and Isaacson (20) had two mild cases of myxedema in which the blood sugar was normal but the glucose tolerance curve was prolonged.

According to Bang (21), glycosuria often follows the administration of thyroid extract and of hypophysis cerebri (dry powder), though not constantly. He states also that the reverse condition, namely, the appearance of glycosuria, takes place after the extirpation of the thyroid gland.

Falta, Newburgh and Nobel (22) showed that after the extirpation of the thyroid gland the injection of adrenalin does not cause glycosuria, but if the administration of adrenalin is combined with the administration of thyroid extract, glycosuria is produced. These authors formulated the hypothesis that the thyroid and the hypophyseal substance cause sensitization of the sympathetic complex to the physiological quantity of adrenalin in the blood.

Cammidge and Howard (23) produced a marked hyperglycemia by the injection of thyroid extract into a fasting rabbit. This hyperglycemia seemed to be directly proportional to the dose of the thyroid extract (Figure X).

Flesch (24) reported 40 cases of hyperthyroidism among which there was not a single case of spontaneous hyperglycemia.

In a study of 27 cases of hyperthyroidism, Geyelin (19) found hyperglycemia in 90 per cent of the moderate and severe cases and even in the mild cases an alimentary hyperglycemia (two hours after the ingestion of 100 grams of glucose) could frequently be demonstrated.

Denis, Aub and Minot (25) made glucose tolerance tests in cases of hyperthyroidism, using normal individuals as controls. In 16 normal subjects—seven females, nine males—their findings ranged as follows:

	Fasting Blood Sugar*	Blood sugar after ingestion of glucose, 100 gm.; bread, 50 gm.; butter, 20 gm.		
		1 hr.	2 hrs.	4 hrs.
Lowest	90	86	84	86
Highest	120	140	120	122

*Blood sugar values in mgm. per 100 cc.

In the 31 cases of hyperthyroidism the blood sugar ranged as follows:

	Fasting Blood Sug.*	Blood sugar after ingestion of glucose, 100 gm.; bread, 50 gm.; butter, 20 gm.			
		1 hr.	2 hrs.	3 hrs.	4 hrs.
Lowest	80	90	97	120	69
Highest	133	232	220	153	140

*Blood sugar values in mgm. per 100 cc.

Among the cases of hyperthyroidism, fasting glycosuria was present in only one; it was questionable in another. The basal metabolism ranged from plus seven to plus 100 per cent. These authors state that there is no definite relationship between the severity of the hyperthyroidism, as expressed by the increased basal metabolic rate, and the degree of alimentary hyperglycemia or glycosuria. In a number of cases in which the tolerance test was repeated after the condition of the patient had been improved by rest and by operation they found that the alimentary hyperglycemia produced by the test meal was less severe than in the first test. They call attention to the possibility of emotional hyperglycemia and glycosuria in hyperthyroidism, as this condition offers notorious examples of nervous instability. These authors conclude that fasting hyperglycemia is very rarely associated with hyperthyroidism but state that alimentary hyperglycemia was observed in every case examined, a statement which requires a definition of what the authors mean by "alimentary hyperglycemia," since to a certain degree this is a normal physiological response.

While these authors found that the fasting blood sugar in hyperthyroidism is within normal limits, Sainton, Schulman and Justin-Besançon (26) found a definite hyperglycemia after the ingestion of glucose or the administration of suprarenin.

Charvat (27) tested the glucose tolerance of patients with hyperthyroidism together with that of controls and reports the following results: In patients with normal thyroids there was either no change of the blood sugar level after the ingestion of glucose or else it was lowered. In cases of hyperthyroidism, on the other hand, with but one exception the blood sugar level rose. (The author does not state the amount of glucose ingested and, moreover, his observations extended for only one hour after

the glucose was ingested, so that it is hard to evaluate his figures.) In discussing his observations the author says:

"That hyperthyroidism affects the blood sugar level is certain, but what is the mechanism of this effect? Does the thyroid exert a direct influence on the sympathetics, on the liver? Or is this influence exerted via the suprarenals? We need not imagine that the increased function of the thyroid (according to the well known diagram of Falta) causes an increased output of adrenalin, for an increased blood sugar is not associated with the glycosuria of hyperthyroidism."

May this correlation perhaps be explained by the fact that thyroid extract sensitizes the liver to adrenalin? The influence of the thyroid might also be exerted via the pancreas. Again and again sclerosis of the islands of Langerhans has been described as present in cases of hyperthyroidism following the extirpation of the gland, and in cases of myxedema, on the other hand, these islands are enlarged. Bodansky (28) produced hypoglycemia by the injection of thyroxin so that we can not rule out this last possibility.

Richardson (29) says that "some patients with exophthalmic goiter are known to respond to the ingestion of glucose by excreting sugar in the urine, and this might be taken as evidence that they are partially diabetic. Observation shows, however, that our patient was able to oxidize the glucose to the same extent as the normal individual."

In 1920 Rohdenburg (3) described two such cases of thyroid diabetes in which glycosuria disappeared after the removal of a portion of the thyroid gland. One of these patients was still sugar-free several years later on a very liberal diet.

Gardiner-Hill et al. (13) in making tolerance tests in a series of 15 well marked cases of myxedema, found decreased tolerance in some, but rarely found glycosuria; they conclude that the renal threshold is raised in this condition. One can not speak of a raised renal threshold in these cases, for it is impossible to interpret the absence of glycosuria during a glucose tolerance test. The probable reason why no glycosuria was observed is the fact that in myxedema the carbohydrate tolerance is increased so that the blood sugar level is raised but little, and even though the renal threshold may lie somewhere between 140 and 180, this level is not reached; consequently there is no justification for the above cited opinion.

Sanger and Hun (30) made glucose tolerance tests, measured the respiratory quotient and calculated the number of grams of carbohydrate utilized in a series of ten cases of hyperthyroidism. Their statement that "it has been shown that in hyperthyroidism, sugar, when it is offered to the tissues as a fuel, is burned with great avidity," seems contrary to my own conception, as does their claim that "the increased utilization of carbohydrate after carbohydrate ingestion, along with the maintained high blood sugar, points toward an inability to store glucose—most probably a failure of liver storage, due to some toxic change in the liver caused by the disease."

To take up the latter problem, it has been shown that a derangement of the liver or even the elimination of the liver does not produce a rise of blood sugar but rather a fall; in fact, fatal hypoglycemia follows complete hepatectomy. Thus, although one might reason *a priori* that when the liver is unable to store glucose the unstored amount would remain in the circulation and thus bring about hyperglycemia, experimental evidence does not support this assumption, since the storage in the muscles is probably increased as the storage function of the liver is diminished. I cannot but feel that a protracted hyperglycemia after the ingestion of a large dose of carbohydrate means that the body is unable to supply insulin in sufficient quantity to transform this carbohydrate into glycogen to be stored in the liver and the muscles, and to bring about its proper oxidation. It has been shown that the stores of glycogen are depleted in hyperthyroidism. Is this depletion due to some interference with the storage of glycogen, as these authors claim, or does it occur because the glycogen has been drawn upon too heavily on account of the markedly increased basal metabolic rate and the consequent increased oxidation of glucose in the body? Hyperglycemia is the result of faulty oxidation of glucose, for we do not find it in many cases in which the basal metabolic rate is high, in which surely the liver glycogen is depleted, but nevertheless the blood sugar remains at the normal level.

These authors have shown by their figures that in a case of hyperthyroidism sugar is burned at a more rapid rate than in a normal individual. This one would expect, for if the total oxidation of the body is increased in cases of hyperthyroidism, as

is shown by the high metabolic rate, then the rate of combustion of carbohydrate must also be increased. Moreover, this higher rate of combustion of carbohydrate will continue until the islands of Langerhans can no longer supply a sufficient quantity of insulin to cope with the increased demand. In other words, in hyperthyroidism there is a hyper-secretion of insulin which lasts as long as the islands of Langerhans can stand the demand on them. In the early stage of hyperthyroidism, as is stated by these authors, there is only this increased metabolic function, a sort of last rush of flames before the fire dies down. Carbohydrate (and protein and fat as well) are burning with a greater intensity, as the R.Q. curve shows, the R.Q. falling only at a later stage when the islands are becoming exhausted and are no longer able to supply a sufficient amount of insulin. This, I think, can be seen from the data given by these authors, from which I have constructed the curves shown in the charts in Figure XI. Thus, for instance, if charts 9, 10, 17, 18 and 20, in which the height and the protraction of the blood sugar curves are but slight, are compared with curves 7, 8 and 16, this relationship can be noted. In other words, the more nearly the blood sugar curve simulates the curve which is characteristic of severe diabetes, the lower the R.Q. curve. I think it is rather hard to interpret the early findings in the borderline cases in which the insulogenic function is not very much reduced. A clear-cut interpretation can be secured only from extreme cases at both ends of the line, on the basis of which the relationships in the cases lying between the two extremes can be interpreted.

Glycosuria and Hyperglycemia Induced by the Ingestion of Thyroid Extract. That the administration of thyroid extract is apt to produce glycosuria is well known. In such a case the glycosuria indicates the presence of hyperglycemia, the degree of which depends in part on the renal threshold of the individual for glucose and in part on an increased toxic permeability of the renal filter. Sometimes, if the thyroid feeding is continued long enough, one can note the same effects as those produced by hyperthyroidism, namely, a higher and a more prolonged rise in the glucose tolerance curve—a type of curve such as characterizes a mild stage of diabetes, or the so-called "functional diabetes."

Von Noorden (31) is of the opinion that thyroid feeding elicits the presence of a prediabetic condition. Glycosuria and the accompanying hyperglycemia, however, are not in evidence in all cases. Thus Becker (32) reports the case of a boy two and one-half years of age who ate 90 tablets of thyroid extract at one time but did not show glycosuria.

On the other hand, Garrod (8) speaks of a youth 18 years of age who probably had no thyroid inadequacy, but after he had taken five grams of thyroid extract daily for about six weeks glycosuria developed. When the drug was stopped the glycosuria promptly disappeared. In another case in which thyroid extract was taken to reduce obesity, at the end of a week sugar appeared in the urine to the amount of four per cent, although only four grams of the thyroid extract had been taken. The glycosuria quickly disappeared after the medication was discontinued. Garrod observed a like result in cases of myxedema which had been treated with thyroid extract. Among 11 myxedematous patients four were found to have glycosuria, and in three of these cases the glycosuria disappeared within a week after the administration of the thyroid extract was discontinued.

In Notthaft's (33) remarkable case (cited by Garrod), a man 43 years of age, on his own initiative, in order to reduce his weight, took about 1000 five grain tablets of thyroid extract in the course of five weeks. Glycosuria was induced and in association with it there appeared the symptoms of Graves's disease — tachycardia, exophthalmos with von Graefe's sign, tremor, and even some enlargement of the thyroid gland. He passed daily over 3000 cc. of urine which contained one per cent of sugar (total excretion of sugar—30 grams). Without any limitation of the carbohydrate intake, the sugar disappeared and thirst ceased after the drug had been discontinued for ten days. Tremor ceased some four weeks later, but the eye phenomena and the swelling of the thyroid gland persisted for about six months.

We may consider such a case as this as one of functional diabetes, since it is accompanied by all the symptoms of early diabetes, viz., thirst, hyperglycemia, glycosuria and polyuria. As soon as the exciting cause, the ingestion of thyroid extract,

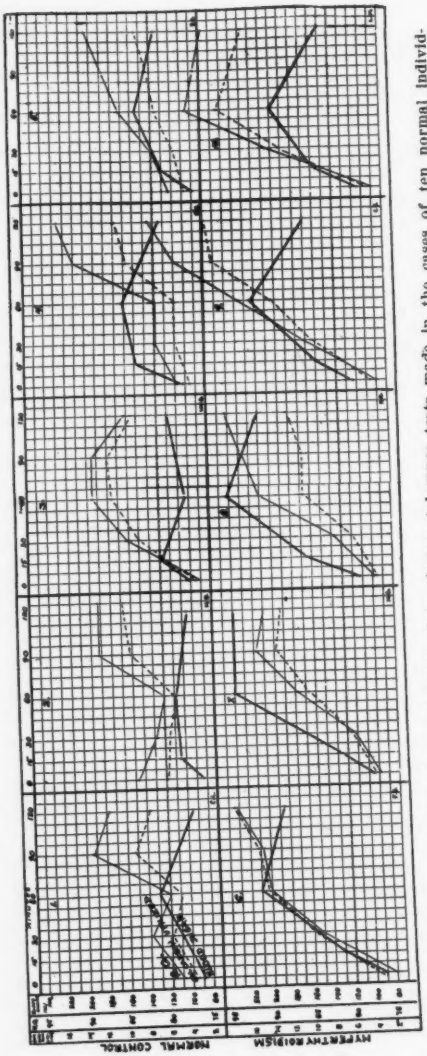

Figure XI (A). A series of curves obtained in glucose tolerance tests made in the cases of ten normal individuals and of ten patients with hyperthyroidism, with synchronous R. Q. determinations and carbohydrate utilization curves. (Plotted from data reported by Sanger and Hun.)

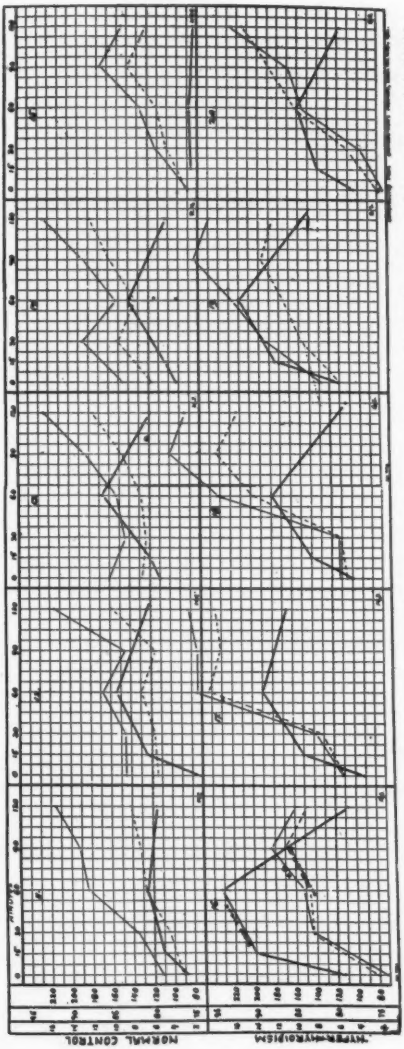

Figure XI (B). A series of curves obtained in glucose tolerance tests made in the cases of ten normal individuals and of ten patients with hyperthyroidism, with synchronous R. Q. determinations and carbohydrate utilization curves. (Plotted from data reported by Sanger and Hun.)

is eliminated, just as when the thyroid gland is eliminated in a case of active hyperthyroidism, the symptoms subside because the islands of Langerhans are not permanently damaged. It is hard to explain such cases by the assumption that in hyperthyroidism the blood contains an over-supply of glucose, when we know that in these cases the liver is glycogen-poor or glycogen-free. Where then would the superabundant sugar come from? The increased postprandial hyperglycemia which occurs in these cases can be explained only by the assumption that the liver of an individual with hyperthyroidism can not properly store glycogen. But as the liver becomes glycogen-poor or glycogen-free, it would appear that a vacuum for postprandial storage should be present. Why then does not such storage take place? Is it because of the lack of insulin? Or does the toxicity of the hyperthyroidism *per se* make the liver cells less able to perform their proper function of glycogen storage? Either of these suggestions would supply a suitable explanation —but that the hyperthyroidism is due to hyper-production of blood sugar does not seem to fit the existing conditions. If there were such hyper-production then this should be most marked in the most severe cases. But such is not the case, at least according to my observations in a large series of severe cases in which the carbohydrate tolerance has been perfectly normal; while, on the other hand, in many a case of mild hyperthyroidism there is a severe derangement of carbohydrate metabolism. If this derangement is due to intoxication affecting the liver, these mild cases should show only a slight carbohydrate disturbance. Consequently, I feel that we must look for the cause of the hyperglycemia in the reserve in the islands of Langerhans in the individual case, a small reserve being easily exhausted, a large reserve resisting even severe hyperthyroidism.

For practical purposes I feel we can consider that the effects of thyroid feeding and of hyperthyroidism are the same. Thyroid feeding therefore gives us an excellent opportunity for the investigation of the effects of hyperthyroidism. Perhaps by persistent experiments with thyroid feeding and by continued clinical observations we may be able to discover whether hyperthyroidism also affects a perfectly normal insulogenic reserve.

This is a practical question. Until recently, I had the feel-

ing that the tolerance of a person with a good insulogenic reserve, as shown by a normal glucose tolerance curve, could not be broken down. Today I feel that I can not make any such positive statement. More data are needed in order that we may see how frequently the exceptions to this conception occur. I can review at least one case in which thyroid feeding did affect and break down a normal tolerance.

Case I (164227): This patient was a married woman 28 years of age. On March 23, 1926, she came to the Clinic because of obesity and shortness of breath. The only significant fact elicited in the family history was that two sisters were stout. She had had none of the usual diseases of childhood, but had had tonsillitis, frequent colds and rheumatism later in life. A curettage had been done in 1917 and tonsil-adenoidectomy in 1923. In 1924 she had a tubal pregnancy and she had had five or six miscarriages. Her weight in 1918 was 105 pounds. (The normal weight for her height, 5 ft. ½ in., would be 118 pounds.) When I saw her she weighed 233 pounds, hence was 97 per cent overweight. Her feet were swollen at times and she had frequent suboccipital headaches.

The only pertinent findings in the physical examination were the following: Blood pressure, 144/90; pulse, 92; visual fields, normal, and no pathological conditions in the retina. The urine showed a faint trace of albumin but no sugar on several examinations. The blood Wassermann test was negative. The blood chemistry findings were: Sugar, 95; urea, 33; uric acid, 4.2; creatinin, 1.3; nonprotein nitrogen, 41.3, and plasma chlorids, 615 mgm. per 100 cc.

During the preceding eight years the patient had increased in weight from 105 to 233 pounds, and during the last three years of this period she had gained 80 pounds. The problem was to decide whether or not we could safely reduce her weight by the usual routine, including the administration of thyroid extract. Thus on March 24, 1926, I made a glucose tolerance estimation which gave a normal curve (see Figure XII—A), and showed that the renal threshold lay above 180 mgm. per 100 cc. The basal metabolic rate at this time was plus 12 per cent, so that it was at the upper normal limit. With these data it seemed safe to institute reducing measures and the administration of five grains of desiccated thyroid substance three times a day was started in April, 1926, and was continued for four months, being discontinued in August because of a rapid pulse. During this time there had been a very slight reduction in weight—from 233 to 228.5 lbs. The patient was seen again in the latter part of November, at which time definite symptoms of hyperthyroidism were present, and the basal metabolic rate was plus 24 per cent. At this time (November 29, 1926) a glucose tolerance test (see Fixure XII—B) showed a definitely de-

creased tolerance as compared with the tolerance at the time of the previous examination, and the renal threshold lay above 236 mgm. per 100 cc., which is contrary to the usual finding in hyperthyroidism.

Thyroidectomy was performed on December 8, 1926, and four months later the patient again returned. Subjectively she had improved, but the pulse rate was still elevated. Her basal metabolic rate at this time was again plus 12 per cent. I made another glucose tolerance test with the result shown in Figure XII—C, which shows a decided improvement over the diminished tolerance shown in B. Her weight had remained the same. An x-ray examination at this time again failed to show any enlargement of the sella turcica.

In brief, in this case the feeding of thyroid substance induced a state of hyperthyroidism which, in turn, produced an early diabetic condition—functional diabetes—so that thyroidectomy had to be resorted to in order to eliminate both the hyperthyroidism and the functional diabetic state.

One can hardly doubt that in this case a state of hyperthyroidism was precipitated by the thyroid medication; furthermore, the glucose tolerance definitely decreased. One can not blame this diminished tolerance on the obesity, for we know that in the course of the preceding eight years the obesity had not lowered the carbohydrate tolerance. Nor can her diet be blamed, as during the period of thyroid administration she was on a minimal diet. This case emphasizes clearly the importance of exercising extreme care in the use of thyroid medication. There is little doubt in this case that had the administration of thyroid substance gone on, a definite diabetic state would finally have been induced.

The Relation of Iodin to Carbohydrate Metabolism in Hyperthyroidism. In 1920 Labbé (34) (cited by Wilder), noted that in cases of diabetes complicated by frank exophthalmic goiter, iodin has a beneficial effect not only on the intensity of the diabetic process but on the exophthalmic goiter syndrome. In Labbé's patient the excretion of sugar, which was 209 grams daily, dropped to 71 grams daily after treatment with iodin, and the palpitation and tachycardia also were favorably affected. Following the suggestion of Plummer and Boothby, in the Cleveland Clinic Hospital Lugol's solution is used in practically the same dosage as that suggested by these authors, i. e., ten minims three times a day until the maximum benefit is obtained. We have noted that the beneficial effects of this admin-

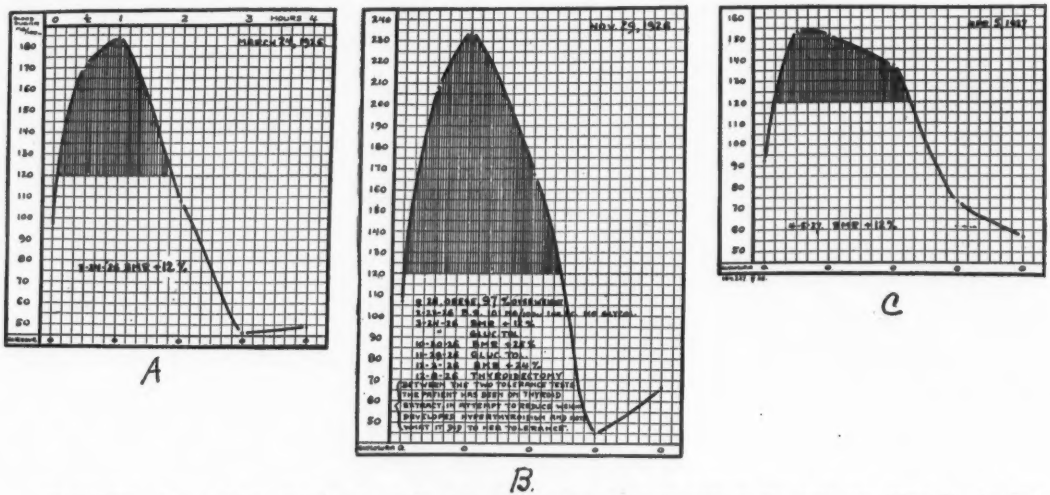

Figure XII. Three charts showing the findings in glucose tolerance tests made in the same case (Case I), the first while the patient's condition was normal except for obesity, the second after the use of thyroid extract, the third after thyroidectomy.

istration continue for from eight to ten days, when the optimum effect is reached, after which time the patient's condition retrogresses. The surgeons have learned by experience that the best time to operate is when this optimum moment has been reached.

Charvat (27) says:

"In our series of cases of hyperthyroidism the blood sugar rose after the injection of iodin and we think that in these cases this was due to an increased function of the thyroid, which was irritated by the sudden influx of iodin. The doses that we injected were so small that the patients did not react to them in any other way. We may assume that these small doses are not sufficient to stimulate a normal thyroid gland to activity. The hyperactive gland, however, is more labile, it is more sensitive to iodin and it is stimulated to specific activity for a time after the injection of iodin by a dose which does not affect a normal gland. We tried to see if by means of a larger dose we could stimulate a normal thyroid to specific action which would manifest itself by a lowering of the blood sugar level. In the single attempt thus far made this seems to be the case, but the changes were so small that they lie within the limits of experimental error.

"We think that the effect of iodin on the blood sugar level in hyperthyroidism probably goes through the following circuit: thyroid—vegetative nervous system—liver. That the liver reacts to stimulation of the sympathetic and parasympathetic nervous systems by the production of glycemia is well known [Bornstein and Holm (35)]. We also know that all substances which can call forth the thyroid effect lead to the washing-out of liver glycogen until it disappears [Abderhalden and Schiffmann (36), Romeis (37)]. That the thyroid has other direct connections with the liver is clear from the experiments of Leone (38), who noted marked changes of the bile (decrease of salts, cholesterin, urea, etc.) after the subcutaneous or the oral administration of thyroid extract to a dog with a gall-bladder fistula. We think further that the mobilization of liver glycogen through the influence of the thyroid gland is not a hormonic process but takes place via the vegetative nervous system, for the changes in the blood sugar level are of short duration and soon disappear."

The effect of the iodin on carbohydrate metabolism is probably a secondary one, that is, the lessening of the hyperthyroidism lessens the total metabolism, which, in turn, lifts part of the extra load off the islands of Langerhans. We must remember that the protein metabolism also is high in these cases and this factor probably contributes to the diminished carbohydrate metabolism.

The Relation of Hyperthyroidism to Diabetes. The coincidence of glycosuria and even of hyperglycemia with hyperthyroidism has already been discussed briefly in a preceding section of this paper.

The earliest report on the relation of the thyroid gland to diabetes was read by Dumontpallier (39) in August, 1867, at a meeting of the Société de biologie. He cited the case of a woman, 22 years of age, with a hypertrophied thyroid, who

TABLE VIII

CASES OF COINCIDENT DIABETES AND HYPERTHYROIDISM REPORTED IN THE LITERATURE

Author	Number of Cases	Total Series of Cases of Hyperthyroidism	Outcome		Year
			Cured or Improved	Died	
Dumontpallier	1	..	..	1	1867
Brunton	1	..	..	..	1874
Hartmann	2	..	..	..	1878
Budde	2	..	..	..	1891
Manges	1	..	..	..	1899
Müller	2	..	..	..	1906
Thompson	3	80	..	..	1906
Sattler	56	From literature	..	25	1909
Crile	1	..	1	..	1915
O'Day	4	..	4	..	1916–20
Rohdenburg	2	..	2	..	1920
Fitz	9	1800 (Mayo Cl.) 315 (M. G. H.)	..	..	1921
Holst	10 (glycos.)	..	10 (by thyroidect.)		1921
Cammidge	1	..	1	..	1923
Buchanan	1	..	1	..	1924
Charvat	1	..	1	..	1926
John	40	93	91	2	1927

complained of marked pulsation of the heart. The case was undoubtedly one of Basedow's disease. Bulimia and excessive thirst had been present for several months. The patient had lost a great deal of weight, had nocturia, and glycosuria—6.2 per cent—and anemia were present. The condition improved after a dietary regimen was instituted, and the urine became less abundant but there was no remission of the symptoms of Basedow's disease. In the winter of 1867 the patient caught cold and died of inflammation of the chest.

The first case of this nature reported in the English literature was that of Landor Brunton (40) in 1874. Hartmann (41) reported two cases from the Tübingen Clinic in 1878. Budde (42) reported two cases in Denmark in 1891, and in 1899 Manges

(43) of New York offered the first report in the American literature.

Von Noorden many years ago described what he termed thyroid diabetes and others [Jacobson (44), Williams and Humphreys (45), Hamman and Hirschmann (46), Hopkins (47), Taylor and Hulton (48), McCaskey (49)], have emphasized the relationship. McCaskey, who investigated the glucose tolerance in some 30 odd cases of exophthalmic goiter, was unable to demonstrate a specific curve of glucose tolerance in the blood during the disease, although he, with others, noticed that there was a slight fasting hyperglycemia in these cases.

In 1906, Friedrich Müller (50) suggested that a special type of glycosuria is related to exophthalmic goiter. His immediate reasons for this belief were drawn from his experience with two cases. The first of these was a case of exophthalmic goiter in which he had given thyroidin, hoping thereby to diminish the size of the thyroid gland. The symptoms of hyperthyroidism did not improve under this form of treatment and sugar began to appear in the urine in increasing amounts. Even after the administration of thyroidin was stopped, the glycosuria did not diminish, and the patient died in coma a few months later. The second case was that of a woman with a chronic goiter in whom diabetes had developed after she had taken thyroid extract for a long time. Some time later the goiter disappeared spontaneously, and, to Müller's surprise, the symptoms of diabetes also disappeared, so that the patient was eventually able to take large amounts of carbohydrate without the production of glycosuria. These two cases were the basis for Müller's statement, reported by Fitz (51), that in the future the thyroid gland should be studied more carefully in its relation to diabetes.

In 1909 Sattler (52), collected 56 reported cases in which diabetes was associated with hyperthyroidism. Thirty-seven of these cases had been followed for a sufficient length of time to afford positive information: 25 cases ended fatally within comparatively short periods of time, and in seven cases the patients died in coma. In the majority of cases the diabetes developed in the presence of a preëxistent exophthalmic goiter, although in

a few cases the incidence of the diabetes seemed to antedate the thyroid disturbance.

In 1915 Crile (53) operated on a man, aged 42 years, with diabetes, in whom, before operation, the daily output of urinary sugar averaged 95 grams. The left and right cervical sympathetic nerves were resected, the left suprarenal was removed and a partial thyroidectomy was performed. Four months later the patient had gained nine pounds in weight and the urine was remaining sugar-free on a diet containing 250 grams of carbohydrate.

In 1916 O'Day (54) reported four cases in which exophthalmic goiter was associated with diabetes. All these patients became sugar-free and recovered a practically normal carbohydate tolerance.

In 1921 Fitz (51) reported an exhaustive study of the relationship of hyperthyroidism and diabetes based upon data collected from the records of the Massachusetts General Hospital and the Mayo Clinic. He says that this combination of diseases is relatively uncommon, but serious. At the Mayo Clinic he found only nine cases of diabetes among 1800 cases of exophthalmic goiter. If we study the time relationship of the onset of diabetes to that of the onset of the thyroid disease in Fitz's series we find the interesting data which I have accumulated in Table IX, data which demonstrate definitely the fact that thyroid disturbance generally antecedes the onset of diabetes.

TABLE IX

THE SEQUENCE IN THE ONSET OF SYMPTOMS OF HYPERTHYROIDISM AND DIABETES MELLITUS RESPECTIVELY

(After Fitz)

Age	Sex	Duration of Goiter Symptoms	Duration of Diabetic Symptoms	Priority of Goiter Symptoms (in Years)	Amount of Sugar Excreted in 24 Hours (in Grams)
51	M	2 yrs.	1 yr. 6 mos.	6 mos.	224
32	F	10 yrs.	2 mos.	9 yrs. 8 mos.	102
49	F	35 yrs.	7 yrs.	18 yrs.	36
47	M	13 yrs.	4 yrs.	9 yrs.	450
53	F	32 yrs.	7½ mos.	31 yrs.	170
54	F	30 yrs.	6 mos.	29 yrs.	32
40	F	7½ mos.	2 mos.	5½ mos.	4%
30	F	7 yrs.	2 mos.	6 yrs. 10 mos.	161
37	F	9 yrs.	3 mos.	8 yrs. 9 mos.	100
44	M	7½ mos.	1 yr.	Reverse	12
57	F	7 yrs.	1 yr.	6 yrs.	72
53	F	40 yrs.	6 yrs.	34 yrs.	80
58	F	40 yrs.	9 yrs.	39 yrs.	30

Fitz concludes that there is no evidence that the coincidence of diabetes and hyperthyroidism is more than a chance occurrence. He believes that the severity of the diabetes in these cases tends to parallel the severity of the thyroid intoxication and that there is no reason for assuming that partial thyroidectomy alone has any curative effect on diabetes. In evaluating this final conclusion we must remember that the cases in Fitz's series were treated in the pre-insulin era.

The presence of glycosuria in cases of hyperthyroidism was described by Chvostek (55), von Noorden (56), von Strümpell (57), and Strauss (58), although these authors found the condition but infrequently. On the other hand, von Noorden has stated that spontaneous alimentary hyperglycemia in cases of hyperthyroidism occurs quite frequently. He thinks that it is absent in cases which present a frankly vagotonic character and when the sympathicotonic phase is in the background.

In twelve cases in which the irritation involved the sympathetic and the parasympathetic systems alike, or in which the sympathetic system was particularly affected, he found fasting blood sugar values of 120-175 mgm. per 100 cc. and a rise of at least 50 per cent in the blood sugar after the ingestion of 100 grams of glucose, but in no case did he find spontaneous or alimentary glycosuria.

Chvostek (59) recognized the frequency of alimentary and spontaneous transitory glycosuria in cases of hyperthyroidism. He thinks that there is no parallelism between the severity of hyperthyroidism and the frequency and severity of the glycosuria. Glycosuria can in no way be counted as a symptom of hyperthyroidism; it merely points, he thinks, to further derangements of the nervous and the chromaffin systems and their influence on the pancreas.

"Pure hyperthyroidism in the presence of a fully normal chromaffin system and a normal pancreas," says von Noorden (60), "will rarely produce an alimentary and spontaneous-transitory glycosuria."

Flesch (24) reports that among his cases of hyperthyroidism 60.7 per cent showed alimentary hyperglycemia of varying degrees of severity; Forschbach and Severin (61), found it to be absent in the majority of their cases. Schulze (62) saw only four cases of alimentary glycosuria among 16 cases of hyperthy-

roidism after the ingestion of 100 grams of glucose (25 per cent).

Allen (63) found that in partially depancreatized dogs thyroid feeding did not aggravate diabetes; he says that no evidence was obtained that diabetes might be caused by overactivity of the thyroid function. In diabetes of moderate severity, deficiency in the thyroid function lowered the hyperglycemia and glycosuria. He concludes that there is no definite antagonism between the functions of the thyroid and the pancreas.

Allen says: "The association of the diabetes with exophthalmic goiter indicates rather plainly that no specific effect of the thyroid over-function is involved, because the association is so uncommon."

In 1912 Garrod (8) in speaking of glucose tolerance in association with hyperthyroidism made the following statement: "Undoubtedly in many cases no diminution of tolerance can be detected, but my own experience leads me to take my stand with those who hold that it is by no means an uncommon phenomenon. In not a few cases spontaneous excretion of sugar, of a transitory or intermittent kind, is observed, if carefully watched for, and in others, as I have already mentioned, persistent glycosuria, with the usual attendant symptoms which go to make up the clinical picture of diabetes."

Hamman and Hirschmann (46) report five cases of hyperthyroidism, in four of which the glucose tolerance curve was typical of diabetes, while in the other it was normal. Glycosuria was present in all five of the cases.

In one case of hyperthyroidism in a patient 52 years of age, the authors present two curves, the first secured before operation and the second one month after operation, the latter showing marked improvement in glucose tolerance.

Lund and Richardson (10) investigated the changes in the blood sugar level which follow operations on the thyroid gland, and make the following statement: "However, practically all patients with a definite elevation in basal metabolism (plus 20 or more) show this reaction" (abnormality of the tolerance curve).

I have not found this to be the case, as an examination of the glucose tolerance curves of my patients will show. In the

series of normal curves, for instance (see TableVI), high basal metabolic rates are associated with normal tolerance curves and vice versa. I hardly feel that we can make a sweeping statement about such a relationship. These two factors (a high basal metabolic rate and a decreased glucose tolerance) may be associated with each other, but, on the other hand, one cannot say that a high basal rate must carry with it a decreased tolerance.

Cammidge and Howard (64) report the case of a woman 47 years of age with a very nervous and high-strung disposition who, in 1913, had suffered from a nervous breakdown. In 1916, while in India, she had a recurrence of this trouble; her urine at that time was sugar-free. In 1917 she began to lose weight, and traces of sugar were discovered in her urine. Her diet was reduced and she was given opiates. The glycosuria subsided and she was allowed to return to a normal diet. In 1918 she had another nervous breakdown, and typical signs and symptoms of exophthalmic goiter developed. While she was being treated for this trouble she was found to be passing large amounts of sugar in her urine and was placed on the "Allen treatment." On the second day of this treatment she became comatose and was unconscious for three days. Eventually the glycosuria ceased and, after three months in the hospital, she was sent home on a restricted diet, free from sugar. In March, 1919, she returned to England and shortly afterward her urine again showed sugar and she resumed her strict diet. For a while she was sugar-free, but later glycosuria returned. In 1920 Cammidge saw her. At that time she had all the characteristic signs of exophthalmic goiter, but there was no polyuria nor thirst. Examination of a twenty-four hour specimen of urine, while she was on a diet of 90 grams carbohydrate, gave the following findings: protein, 85 grams; fat, 80 grams; sugar, 70 grams; no acetone; creatinin, 4.4; amino-acid nitrogen, 0.5; total nitrogen, 19 mgm. per 100 cc. A serial analysis of the patient's blood made on this date after a test breakfast is presented in Figure XIII. This shows fasting hyperglycemia and the curve indicates diabetes, as does, in fact, the fasting blood sugar. Cammidge thinks that "the subsequent concurrent course of the difference value and sugar curves was in favor of the hyperglycemia being chiefly dependent upon disturbance of the func-

tions of the other ductless glands or of the nervous system, and in view of the clinical signs, it seemed likely that the thyroid was mainly at fault." Glycosuria diminished as the diet was diminished until the patient again became sugar-free. The diet was finally raised to carbohydrate, 60 grams; protein, 60-65 grams; fat, 90 grams. On this she maintained her weight and the urine remained sugar-free. She was last seen in March, 1921, up to which time she had had no glycosuria; at this time her blood sugar, two hours after a meal, was 160 mgm. per 100 cc. The authors say nothing as to the further development or subsidance of the hyperthyroidism.

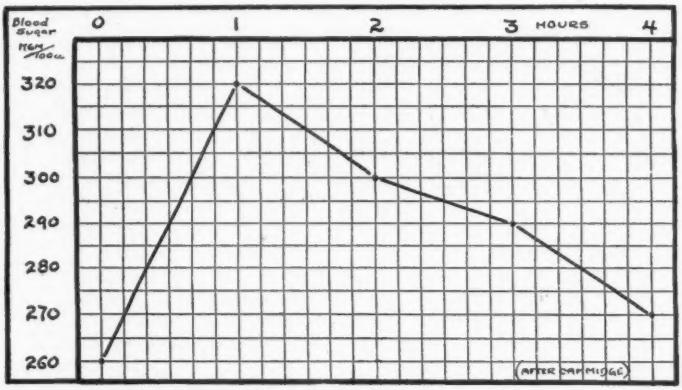

Figure XIII. Chart showing findings in a glucose tolerance test in a case of hyperthyroidism reported by Cammidge.

We have here a case of diabetes, the onset of which was preceded by hyperthyroidism, if we may consider the nervous breakdown to have been the beginning of hyperthyroidism, as the later course of events appears to prove was the case. Diabetes does not cause hyperthyroidism, but hyperthyroidism can, and I believe always does, bring to light a latent form of diabetes.

As for the incidence of diabetes associated with hyperthyroidism, but few figures are available. Sattler (52) found diabetes in three per cent of his series of cases of hyperthyroidism (in two-thirds of these cases the hyperthyroidism preceded the onset of the diabetes). Among 1000 cases of diabetes von Noor-

den (65) found 6 cases of frank hyperthyroidism and from 20 to 25 cases in which symptoms of hyperthyroidism appeared.

According to von Noorden the prognosis of these cases is poor. Sattler cites a mortality of 60 per cent among his cases of hyperthyroidism with diabetes.

Von Noorden mentions also the marked cardiac weakness in this combination of diseases, this being much more marked than is the case in uncomplicated cases of either diabetes or hyperthyroidism.

In hyperthyroidism, sweating (vagotonic) is a frequent symptom; it is absent in the less frequent sympathicotonic form. Grawitz (66) pointed out that this symptom often is absent when hyperthyroidism is combined with diabetes.

Von Noorden (67) says:

"Whether a thyrotoxic weakening of the pancreas hormone is present or whether the thyrotoxic excitation of the chromaffin system is the cause of the hyperglycemia need not be determined; the latter explanation is, after all, improbable, since the sensitivity of the liver cells to hyperadrenalism becomes greatly weakened if the latter condition is of long duration. The findings of W. Cramer and R. A. Krause seem to show that thyrotoxic influences are really determinative: In their experiments, when the animals were fed with fresh thyroid gland substance the livers became practically free from glycogen after a few days."

It seems from the above that hyperthyroidism favors glycogenolysis. In the animal experiments this is quite definitely proven to be the case. In man the regulatory mechanism plays a part, when the irritability of the sympathetic and of the parasympathetic systems work in harmony; the greater the irritability of the sympathetic, the lighter the disturbance of the sugar output and vice versa. In hyperthyroidism, however, according to von Noorden, we deal but rarely with a pure hyperthyreosis. We can consider it as certain that frequently functional disturbances of other endocrine organs are concerned in the production of this syndrome, and because of their interrelationship and influence on the pancreas and on the chromaffin system the primary irritation from the hyperactivity of the thyroid must have a definite influence on the sugar-forming function of the liver.

Von Noorden (68) summarizes the relationship of the thyroid gland to carbohydrate metabolism as follows:

"1. After the administration of thyroid gland by mouth or by subcutaneous injection (in rabbits or dogs), glycosuria appears frequently. This disappears after the administration of the thyroid gland is discontinued. Similar observations have been made in man, although all observers have been struck by the fact that the reaction of the human organism differs according to the individual. In some human cases a lasting glycosuria appeared after a brief period of feeding with thyroid extract (true diabetes); it is possible that in these cases there was a prediabetic condition which was first discovered after the feeding (von Noorden).

"2. In many non-diabetic individuals tests for alimentary glycosuria give positive findings after thyroid feeding, whereas they give negative findings before the feeding. Even if no glycosuria is produced, hyperglycemia usually develops (my own experiments) and in animal experiments the glycogen disappears from the liver.

"3. When thyroid substance is administered to diabetic individuals, their glycosuria is increased: This, however, is noticeable only in light cases; in severe cases the difference is too slight to be significant. The blood pressure rises at the same time (Falta), which is not the case when thyroid substance is fed to non-diabetic individuals. This is probably due to an irritation of the chromaffin system which in many diabetic patients is in a state of hyperirritability.

"4. In Basedow's disease (hyperthyroidism) the assimilation level for glucose is frequently lowered. A considerable degree of glycosuria may appear after the ingestion of 100 grams of glucose (10-15 grams). According to Eppinger, in cases of hyperthyroidism in which the signs of an increased sympathetic irritability are present one can expect to find glycosuria, whereas in those cases which present signs of more marked vagus irritability alimentary glycosuria is not present.

"5. In dogs after thyroidectomy the assimilation level for glucose is very high and the subcutaneous injection of adrenalin in quantities which under normal conditions produce glycosuria is without effect. A heavy carbohydrate intake also fails to produce glycosuria. The animals will present glycosuria, however, if, together with the injection of adrenalin, a thyroid substance is injected (Eppinger, Falta, Rudinger). Other authors (Underhill, Hilditch, Böe, Blum) failed to confirm these findings and their observations deny any connection between the thyroid gland and carbohydrate metabolism. Nevertheless, it does not follow that we should disregard the investigations of Eppinger and his assistants, which were doubtless carried out with the greatest care. In my opinion they continue to be valid and the divergent results of the later tests must be explained. . . . If the parathyroids are removed or injured, tetany (frank or latent) is produced, on the one hand, and a considerably lowered level of the assimilation of carbohydrate on the other (Hirsch, Un-

derhill, Saiki). In this respect the action of the thyroid and of the parathyroids is antagonistic, and when both are removed the effect of the removal of the latter predominates.

"6. In the diseases of myxedema (hypothyroidism and dysthyroidism) the assimilation level for glucose is raised (Hirschl, Knöpflmacher, Ewald, Aschenheim). . . . In one case, recently observed, 250 grams of glucose were taken within about half an hour, and 250 grams of bread one hour later, but no glycosuria occurred. (N. B.—Such cases have an abnormally high tolerance for carbohydrate.) In three cases of marked thyrogenic adiposity in children from 12 to 14 years of age the fasting blood sugar values were 60-70 mgm. per 100 cc. . . . [See also John (69): 'Glucose tolerance and its values in diagnosis,' and note the glucose tolerance curves in hypothyroidism.] One cannot expect always to find such low values. In these cases there are often changes in other endocrine glands which work antagonistically. In four cases of thyrogenic adiposity in adults the following blood sugar values were found: 106, 109, 112 and 117 mgm. per 100 cc., respectively."

The above discussion suggests that thyroid hyperglycemia is due either to increased sugar production or to decreased sugar utilization. A third factor which must be considered is the inability of the liver to store glycogen, since in hyperthyroidism the liver is either glycogen-free or glycogen-poor. If sugar production were the only factor concerned, then hyperglycemia would be more marked in the most severe cases of hyperthyroidism, that is, in those in which the basal metabolic rate is most increased, and this is not the case. The seat of the trouble, then, must be sought elsewhere, and I feel that, as in any case of persistently increased glycemia, the primary cause is a decreased insulogenic capacity of the islands of Langerhans, which, in some cases, whatever the basal metabolic rate, cannot cope with their task so that carbohydrate metabolism begins to lag.

The livers in these cases are practically free from glycogen [see Cramer and Kraus (70)], thus there should be a ready storage place for the ingested sugar which would obviate an increase in the blood sugar, but this apparently does not happen in a considerable percentage of cases. Why? Has the insulin also something to do with the storage of glycogen in the liver? Or is the glycogen burned as fast as it is formed by the increased metabolism? Perhaps both of these are factors.

Boothby and Wilder (71) point out the clinical importance of recognizing the possibility that exophthalmic goiter may be a complication in cases of diabetes in which the ordinary measures of treatment by insulin seem not to be effective.

By the intravenous injection of glucose at uniform rates Wilder and Sansum (72) have shown that, whereas in normal individuals glucose can be injected intravenously at a rate of 0.8 gram per kgm. per hour without the development of glycosuria, glycosuria may appear in patients with hyperthyroidism when only 0.6 grams or even 0.5 grams of glucose per hour per kgm. are injected. In a later communication Wilder (73) states, "All such observations show that in hyperthyroidism the rate at which the body can assimilate glucose may be disturbed; they do not prove that anything is at fault with oxidation or reduction. Therefore, they do not indicate the existence of diabetes." This statement, however, is based solely on the presence or absence of glycosuria at different rates of glucose injection and, therefore, is valid only if it can be proved that in the cases of hyperthyroidism in which glycosuria appears only the permeability of the kidney for sugar is changed. No evidence is offered on this point, as synchronous blood sugar findings are not given. Moreover, to prove this statement, it must be proved that the renal threshold in such cases is lowered. This would require knowledge of the renal threshold before and at the time the hyperthyroidism developed. As to the exact height of the blood sugar at which glycosuria occurs we can offer no general rule, since the threshold varies widely even in normal individuals. We must conclude, therefore, that if glycosuria occurs (with the exception of its occurrence in individuals with very low thresholds in whom glycosuria is practically always present) that it is due to hyperglycemia—the glycosuria being but a secondary phenomenon. That this point is actually verified by Wilder's figures is illustrated by the chart shown in Figure XIV, which I have constructed from Table 3 in his article. This chart clearly demonstrates that glycosuria occurred only in the presence of hyperglycemia. It follows that if in any case a postprandial hyperglycemia is of longer duration than normal postprandial hyperglycemia, it must be concluded that there is not enough insulin available

to oxidize or reduce and store the increased sugar in the blood, in spite of the statement by Wilder that "they do not prove that anything is at fault with oxidation or reduction."

Wilder reasons further that "there is indeed good evidence to show that the utilization of carbohydrate is actually accelerated by hyperthyroidism in patients who do not have true diabetes. Following test meals of glucose in patients with exophthalmic goiter, as DuBois (74) and also Sanger and Hun

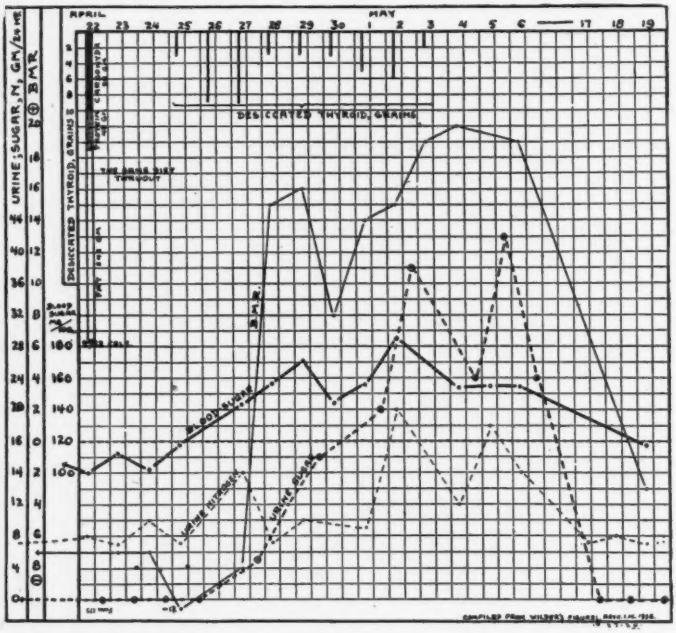

Figure XIV. Synchronous blood sugar, urine sugar and basal metabolic rate findings before and after the administration of thyroid extract. (Compiled from Wilder's figures.)

(30) have shown, the respiratory quotients rise more abruptly than is normal." This is true, but this statement has no direct bearing on the problem of the relationship of diabetes to hyperthyroidism, as in cases of non-diabetic hyperthyroidism we may assume that the insulogenic apparatus is intact and has still a large reserve whereby to cope with any situation with which it

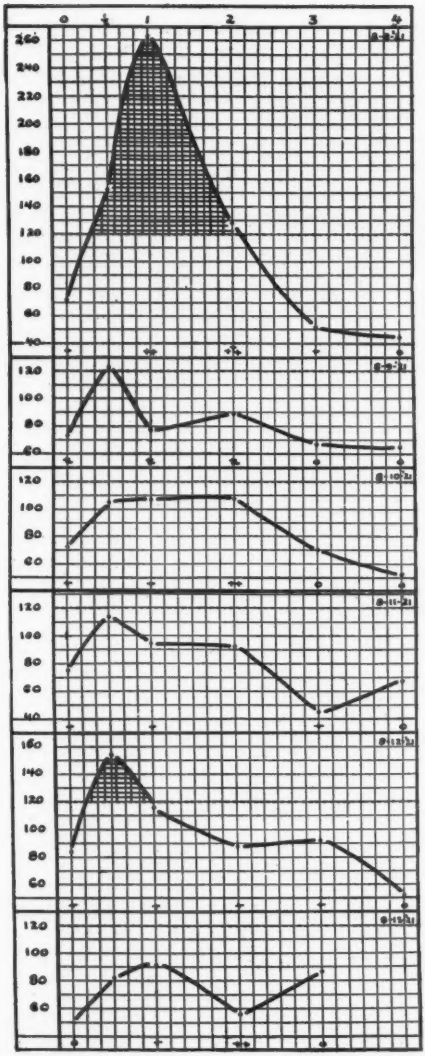

Figure XV. Charts showing the curves obtained in six glucose tolerance tests made on the author on six successive days. Note the progressive increase in the utilization of glucose.

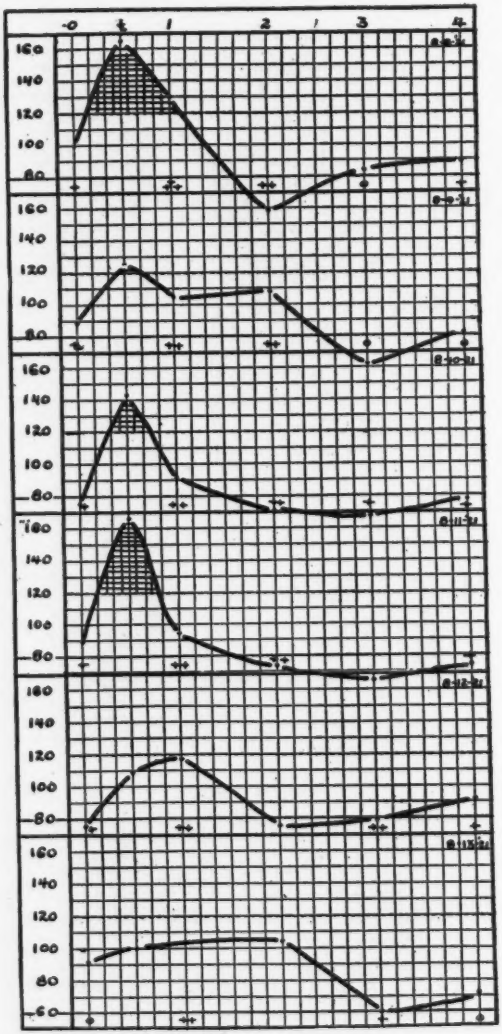

Figure XVI. Charts showing the curves obtained in six glucose tolerance tests made on the author's assistant (A. R.). Note the progressive increase in the utilization of glucose.

may be confronted. It has been shown that if a normal individual ingests abnormal amounts of carbohydrate daily for a period of time, the output of insulin will be quickened by this constant teasing, so that at the end of a week the response of the islands of Langerhans to the ingested glucose is more prompt than it was at the beginning.

In this connection I can cite an experimental study of which one of my assistants and I were the subjects. Daily glucose tolerance estimations for six successive days gave the results shown in Figures XV and XVI. It will be noted that the tolerance curve of each of us was lowered almost daily, so that at the end of the week each curve showed but a slight rise, an observation which indicates that the islands were responding more promptly to the stimulus of the ingested glucose than at the beginning of the experiment. We can assume that a similar condition exists in cases of hyperthyroidism in which the insulogenic apparatus is unimpaired. The metabolism of these patients is increased by the hyperthyroidism. As a rule, they eat voraciously, thus consuming a large number of calories; they have a special craving for sweets. The increased carbohydrate intake calls daily for an increased output of insulin, and such an increased output takes place as long as the islands can well supply the demand. As the result of the increased output of insulin, increased oxidation takes place and more glucose is burned per unit of time. In some cases the insulogenic function can control this increased activity uninterruptedly, and the respiratory quotient is increased until the patient is operated upon or treated in some other manner, when the hyperthyroidism subsides and the carbohydrate metabolism shifts back to the normal rate. But there are other cases in which the insulogenic reserve is not sufficient; or the increased metabolic strain continues so long that the insulogenic apparatus breaks down to a greater or less degree under the added strain—and there results first a slight disturbance of the carbohydrate metabolism which, if not relieved, becomes more marked until eventually a frank case of diabetes develops. The first step in this process, therefore, is the increased rate of function which, in some cases, goes on to the second stage and, in some, on still further until complete exhaustion of the islands occurs, just as any other organ

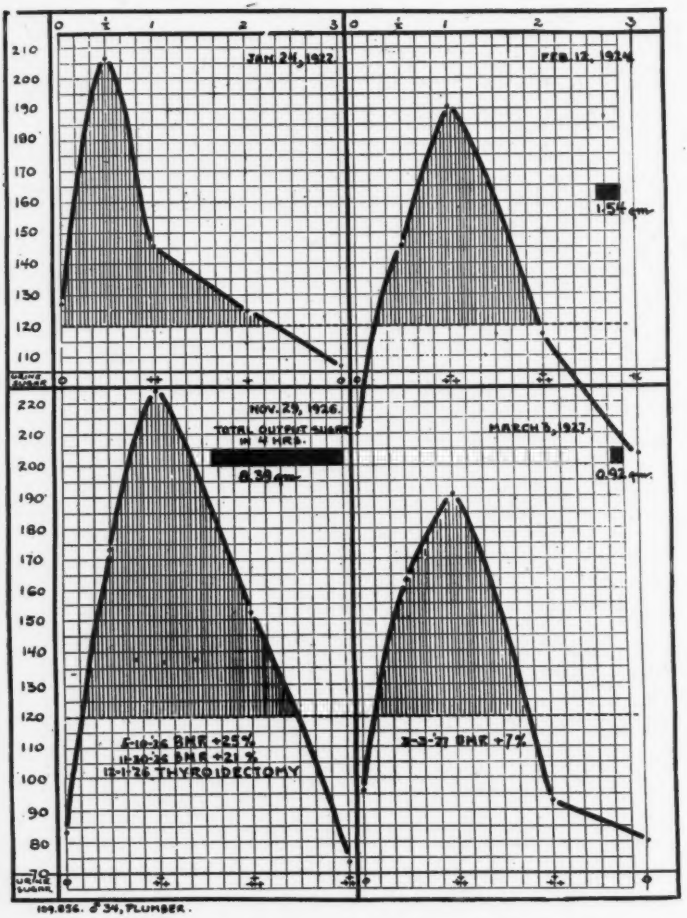

Figure XVII. Charts showing the findings in four glucose tolerance tests made in a case of hyperthyroidism (Case II). The first two curves were obtained when the patient's condition was normal, the third after the development of hyperthyroidism, the fourth after thyroidectomy had been performed.

of the body may become exhausted as the result of continuous hyperfunction.

This point is emphasized further by the fact that if we remove the thyroid gland in a patient in whom the carbohydrate tolerance has been decreased through the influence of hyperthyroidism, so that a mild type of diabetes has developed, the carbohydrate tolerance is improved (see Figure XVII). It would be interesting if we could have data regarding the condition of the islands of Langerhans during these successive stages in order that we might have *prima facie* evidence whether or not in these early stages the hydropic degeneration of the beta cells is demonstrable. But as patients do not die in these early stages, such final evidence cannot be secured. It certainly seems, however, as though we had sufficient clinical evidence to conclude that in every case of diminished carbohydrate tolerance the insulogenic processes are identical.

The following case-history is offered as presenting corroborative evidence of this conception that the insulogenic function may be progressively weakened by hyperthyroidism and in part, at least, restored by the removal of the thyroid gland.

Case II (109856): The patient was a man 34 years of age. He had been married for 10 years and had two healthy children. There was nothing relevant in the family history. He had always been in good health and had had no previous diseases excepting influenza. When I first saw him on January 21, 1922, he stated that two years before he had been examined by his family physician who had made a diagnosis of diabetes and had prescribed a diabetic regimen. Since that time no blood sugar examinations had been made, but the patient had been examining his own urine and had occasionally found sugar. He had lost 12 pounds in weight. He did not have thirst or frequency of urination. He presented the appearance of a man in perfect health except for the evidence of anxiety about the diabetes.

I made a glucose tolerance test on January 24, 1922, which gave a normal curve (Figure XVII) and showed a low renal threshold. I prescribed a heavy diet, rich in carbohydrates, for two weeks, and asked him particularly to eat an abundance of sweets during this period, at the end of which the fasting blood sugar was only 87 mgm. per 100 cc. and he had no glycosuria.

Periodic blood sugar and urine examinations gave the following findings:

Date		Blood Sugar mgm. per 100 cc.		Urine Sugar
1922	1-24	128		negative
	2-24	104		
	5-24	111		negative
	11- 1	102		plus
1924	2-11	97		negative
	2-12	80		
1926	2-17	87		negative
	3-22	78	(1½ hrs. p. c.)	2 plus
	6- 2	95	(5 hrs. p. c.)	
	11-29	83		negative
1927	3- 3	96		negative

Throughout this period the man had been working hard and his diet had been like that of any normal individual.

In 1926 the patient grew restless, was quite nervous and did not feel well. Someone told him that he had a goiter, which frightened him and he consulted several physicians. He was told by the first physician consulted that he had hyperthyroidism and should be operated upon at once. The second consultation was with another internist who was quite definite in his statement that his trouble was neurosis and not hyperthyroidism (the patient was a Jew) and that an operation was not indicated. At that time his basal metabolic rate was found to be plus 25 per cent. He next consulted a surgeon who also did not consider this to be a case of hyperthyroidism and advised against operation. He consulted another surgeon who said he had hyperthyroidism and should be operated upon.

With this story he came to me asking for advice. One surgeon and one internist advised operation, another surgeon and another internist advised against operation. I found the basal metabolic rate to be plus 21 per cent and referred the patient to the surgical division for operation, following which all his symptoms subsided and he is now back at work and in perfect health.

While the above data are interesting, the point of special interest is found in the following findings: I made four glucose tolerance tests in this case during five years (Fig. XVII). Of these, the first two demonstrated that no diabetic condition was present. In 1926 hyperthyroidism developed and the blood sugar, though it returned to the normal level in less than three hours, nevertheless indicated a diminished insulogenic function. That is, as is shown by the height and length of the curve, the blood was flooded with sugar for two and a half hours and

sugar was excreted through the urine. This indicated that the carbohydrate tolerance had become diminished, or in other words, that the insulogenic function had begun to lag. According to our conception, the man was on the way toward diabetes unless the strain should be lifted. It was a comparison of this curve with the two that preceded it which made me decide that an operation was indicated, as I felt that by the removal of the thyroid gland we might be able either to restore the insulogenic function to its former status or at least to prevent further damage. Did we accomplish this? Note the curve made March 3, 1927, as shown in Figure XVII, which was made three months after the thyroidectomy! This demonstrates a definite improvement in the patient's carbohydrate tolerance, a return to the normal.

These curves appear to demonstrate (1) that hyperthyroidism exerts a destructive influence on the insulogenic function and (2) that the insulogenic function may be restored to normal or its further damage prevented by the removal of the thyroid gland.

That one cannot afford to disregard the presence of even slight glycosuria or of a slight degree of fasting hyperglycemia in patients with hyperthyroidism is well illustrated by the following case. Many patients of this type have fully developed diabetes which would go on unrecognized if one were looking for the classical picture of that disorder. The classical symptoms of diabetes are present only in well advanced cases, or in cases in which the onset is acute; the early cases, and those in which the onset is gradual, show few or no signs of the disease.

Case III (176410): The patient was a married woman 59 years of age. There was no familial history of diabetes or of thyroid disease. The patient had had measles, mumps, chicken pox, scarlet fever, whooping cough, tonsillitis and influenza. She had had two pregnancies and had one child living and well, the other having died soon after birth. When I first saw her on December 1, 1926, she complained of rapid heart, nervousness, loss of weight and goiter. Three years before, in 1923, she had had hyperthyroidism which had been treated by eight injections of boiling water into the gland, after which the symptoms had disappeared and she had been in good health until about May, 1926. Since the latter date she had been feeling very tired, the heart action had become rapid, she did not sleep well and never felt rested. Her appetite was poor, she had "gas on the

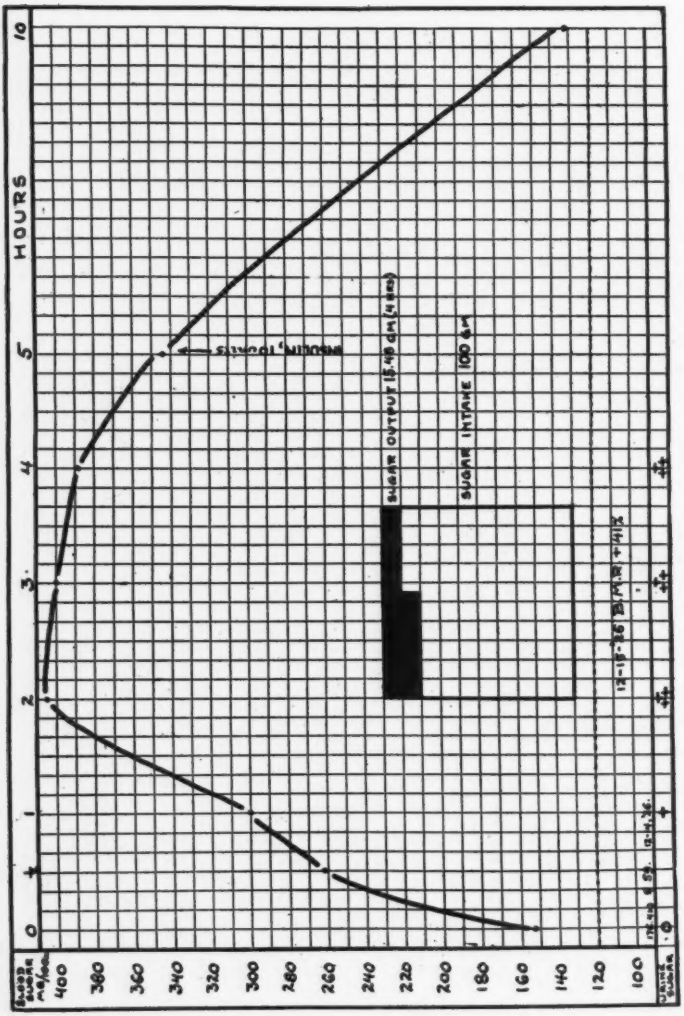

Figure XVIII. Chart showing the findings in a glucosemia at the time when this test was made. thyroidism (Case III). Although traces of sugar had been found in the urine previous to our examination, there was no fasting glycosuria and only a slight fasting hyperglyce tolerance test made before operation in a case of hyper-

stomach" and was constipated. During the preceding four months she had lost 36 pounds and was considerably underweight. She had been in bed at various times during the preceding 10 or 12 weeks. She complained also of pain in the precordium radiating to the left arm. Physical examination and laboratory examinations gave the following pertinent findings: A definite adenoma with hyperthyroidism; glycosuria; blood sugar on three consecutive mornings—respectively 169, 172 and 153 mgm. per 100 cc., 3 hours p.c.; pulse rate, 88; blood pressure, 150/70; basal metabolic rate, plus 41 per cent.

This was obviously a second attack of hyperthyroidism in a woman past the menopause. As compared with the elevated basal metabolism, the moderate glycosuria and slight increase in the fasting blood sugar would seem of little importance, but nevertheless I made a glucose tolerance test on December 14, 1926, the results of which are shown in Figure XVIII.

Although the fasting blood sugar was but 153 mgm. per 100 cc. and there were no glycosuria and no classical symptoms of diabetes, yet, as may be seen on the chart, the blood sugar rose to 405 mgm. per 100 cc. during the second and third hours of the test and was still at 344 mgm. per 100 cc. at the fifth hour, when ten units of insulin were given intravenously; and even with the aid of insulin, the blood sugar did not reach the normal level before the tenth hour.

A thyroidectomy was performed on December 16th, 1926. Urinary analyses of 24 hour specimens while the patient was in the hospital gave the following findings:

Date		Vol. cc.	Sp. grav.	Sugar	Acetone
December 1, 1926				4 plus	
4,			1030	4 plus	
8,			1030	4 plus	
12,		2150	1007	neg.	2 plus
13,		575—	1013	neg.	2 plus
16,	(thyroidec-	1725	1005	neg.	
17,	tomy)	1200	1010	trace	2 plus
18,		550—	1015	neg.	2 plus
20,		1550	1006	neg.	neg.
21,		1425	1008	neg.	2 plus
22,		950	1010	neg.	2 plus

During her stay in the hospital she was on a diet of carbohydrate 100 grams, protein 60 grams, fat 128 grams—a total of 1800 calories. The fasting blood sugar examination gave the following findings:

Date 1926	Fasting Blood Sugar mgm. per 100 cc.	Insulin dosage (in units)	
December 11	172		
12	159	10	
13	147	10	
14	153	10-10	
15		10-10	B. M. R., plus 41 per cent
16	133	10	Thyroidectomy
17	221	10-10-10	
18	158	10-10-10	
19	124	10-10-10	
20	84	10-10	
21	113	10	
22	114		
23	112		Discharged from the hospital.

Following the thyroidectomy and with the help of a little insulin, the blood sugar returned to a normal level, where it has remained even since the insulin has been discontinued.

The importance of fasting blood sugar tests in the presence of hyperthyroidism is well illustrated also by the following case:

Case IV (144,190): The patient was a young Jewish woman, 21 years of age, who was first seen by me on November 18, 1924. Her father had died of diabetic gangrene and one sister had diabetes. She was very nervous and irritable and had crying spells and palpitation of the heart on the slightest exertion. These symptoms had been increasing during the preceding two years. She had lost 20 pounds in weight; easily became fatigued; had had abnormal thirst and polyuria for a year. She formerly had eaten large quantities of sweets. She had been examined 6 months before in New York and no glycosuria had been found.

On examination I found that the patient presented a typical case of hyperthyroidism. Her basal metabolic rate was plus 31 per cent. Her blood sugar was 600 mgm. per 100 cc.; CO_2, 38.5; plasma acetone, 3 plus; glycosuria, 3.3 per cent. The Wassermann test was negative. Although we had no definite data regarding the onset of the diabetes, it was evident that the hyperthyroidism had existed for two years and undoubtedly had preceded the diabetes.

The basal metabolic studies in this case can be summed up as follows:

Date	B. M. R. %	Place
April, 1924	Plus 23	New York
November, 1924	Plus 31	Cleveland Clinic
December, 1924	Plus 30	New York
April, 1925	Plus 65	New York
April, 1925 (1 week later)	Plus 45	New York

The patient went back and forth between New York and Cleveland and consequently I did not see her frequently. She took large

amounts of insulin (60 units A. M., 50 units P. M.), and I had the impression that she did not adhere closely to her diet. She was in several hospitals at various times, and at one time went into coma, but recovered and continued, so to speak, to "drift along." She was not operated upon, but in New York received x-ray treatments over the region of the thyroid gland. I saw her for a few minutes in 1926, at which time she seemed to be all right, much of her nervousness having disappeared.

On January 16, 1927, she had a miscarriage and was taken to a local hospital. On the following day coma developed and she died. At that time she had a high blood sugar (256 mgm.); white count, 36,000; blood culture negative. A postmortem blood culture was not made. The patient was quite edematous at the time of her death.

In this case the symptoms of hyperthyroidism had somewhat subsided, but whether this was due to the x-ray treatments or to the use of insulin is hard to say. The important point is that the accident of miscarriage supervening upon an uncontrolled, severe diabetic condition was sufficient to bring about the end.

Had thyroidectomy been performed in time in this case, would that have relieved the strain on the islands of Langerhans and saved the patient from the development of diabetes? And if the diabetes had been discovered at an earlier stage and a proper regimen established would the fatal outcome have been avoided? Since the status of the carbohydrate metabolism before the development of hyperthyroidism is not known in this case, it is impossible to tell the sequence of the diseases. Was the patient a prediabetic and thus a prey to any disturbance which would precipitate diabetes, the disturbance in this case being hyperthyroidism? Or was her carbohydrate metabolism normal and did the diabetes develop in spite of it, as the direct result of the hyperthyroidism? A study of this case shows how essential it is that we investigate the carbohydrate metabolism in a large series of normal individuals in order to determine whether a normal carbohydrate tolerance can be broken down, or whether it is only in the case of a diminished carbohydrate tolerance that the system gives way under a strain.

In 1926 Marsh (75) discussed the relation of glycosuria to thyroid disease. He states that glycosuria is encountered in about two per cent of the cases of hyperthyroidism; but believes that two types of glycosuria occur in these cases: (1) symptomatic glycosuria; (2) diabetic glycosuria. Marsh tried

to differentiate these two types by the estimation of the R.Q. rather than by glucose tolerance estimation, although he also employed the latter measure. If, following the administration of a large dose of glucose the R.Q. rises to 90, he considers such a case to be non-diabetic. In the first case in his second table he offers the following findings from a glucose tolerance test and R.Q. determinations in a case of exophthalmic goiter:

		Periods after ingestion of glucose		
	Fasting	1 hour	2 hours	3 hours
Blood sugar mgm. per 100 cc.....	136	370	270	214
R. Q.	0.71	0.75	0.90	

The case was that of a man 32 years of age, who for six weeks had had polyuria, polydipsia, nervousness, palpitation of the heart and weakness, and had lost 33 pounds in weight. He had exophthalmos, lid-lag, difficulty of ocular convergence, goiter with thrill and bruit, a systolic murmur over the entire precordium and a fine tremor of the extended fingers. The basal metabolic rate was plus 38 per cent; pulse rate, 92; blood pressure, 124/60. He was excreting 11 grams of sugar in 24 hours, and his blood sugar was 420 mgm. per 100 cc. Glycosuria disappeared while he was on hospital diet, and he left the hospital sugar-free, with a basal metabolic rate of minus eight per cent. Marsh interprets the hyperglycemia and glycosuria in this case as due to a defect in carbohydrate mobilization rather than to a defect in the carbohydrate combustion, as is the case in true diabetes. At the end of his article Marsh makes the following statement: "The symptomatic glycosuria of hyperthyroidism demands no special management. The patient may be given a liberal diet and the defect in his carbohydrate metabolism ignored." (Note that he uses the term—"defect in carbohydrate metabolism.") "Treatment is directed at his thyroid disease, and as the latter is controlled, the glycosuria may be expected to disappear. Diabetes, on the other hand, demands very careful management."

If we are to accept Marsh's conception, where are we to draw the line between diabetic and non-diabetic hyperglycemia and glycosuria? Are we to disregard such classical symptoms of diabetes as hyperglycemia, a blood sugar of 420 mgm. per 100 cc., and the excretion of 11 grams of sugar, because of the

recent development of the symptoms of diabetes, which indicates that the islands of Langerhans are only functionally impaired? If we were to follow this rule we should have to rule out all mild and functional cases of diabetes whether or not they are associated with other diseases. Such a consideration as that offered by Marsh would, I fear, only tend to throw the whole problem of the differential diagnosis of diabetes into complete chaos. Why does Marsh advocate the glucose tolerance test as a means of differentiating the thyroid glycosuria from diabetic glycosuria and then disregard his own figures? Should a blood sugar figure of 214 mgm. per 100 cc. at the end of the third hour of a glucose tolerance test be disregarded, just because the case is one of hyperthyroidism? In Marsh's second case, in addition to high blood sugar figures (210-460) there was also an impairment of the R.Q. Any functional diabetic will present this additional evidence if he is allowed to remain untreated for a long enough period, just as he will show diminished blood sugar and a better R.Q. if he receives prompt treatment.

If one makes blood sugar examinations in any series of cases of hyperthyroidism one often finds: (1) a mild degree of hyperglycemia in the fasting blood; and more frequently (2) that the blood sugar is above 120 mgm. per 100 cc., three or more hours after a meal. This second value is the deciding point in making a diagnosis of diabetes or of an early disturbance of carbohydrate metabolism, for if the insulogenic function is normal then hyperglycemia will not be present three hours after a meal. Diabetes associated with hyperthyroidism or due to hyperthyroidism does not differ from diabetes due to any other cause, it is diabetes, and if unrecognized or disregarded, it will probably become severe in time. On the other hand, if the tendency to hyperglycemia is recognized early and receives prompt treatment, then the primary diabetic tendency will often disappear completely. Because of the fact that the glycosuria or hyperglycemia, or both, which are associated with hyperthyroidism often disappear after thyroidectomy, many authors have not been willing to recognize this condition as diabetes, but prefer to regard it as merely a temporary functional disorder of carbohydrate metabolism, which disappears after the removal of the thyroid gland. Were we to accept this

point of view in regard to hyperthyroidism, then we should have to do the same in all other cases in which hyperglycemia and glycosuria, whatever their origin, disappear. In other words, we should have to disregard as cases of diabetes all those in which the hyperglycemia is functional in type.

"Functional diabetes," as manifested by what may prove to be a transient hyperglycemia, exists because the islands of Langerhans have been slightly damaged, i.e., have undergone the so-called hydropic degeneration which, as Copp and Barclay (76) have demonstrated, is still a reversible process. In such cases by simply removing the cause of the over-loading of the insulogenic function we can clear up the condition. Thus when the thyroid gland is the causative factor, then thyroidectomy may result in the restoration of the insulogenic function, that is, it will cure such cases of "functional diabetes" as are associated with hyperactivity of the thyroid gland. The effect of thyroidectomy, therefore, instead of proving that hyperthyroidism bears no etiological relation to diabetes, on the contrary, offers strong proof that it is a potent etiological factor.

Does Marsh believe that cases in which glycosuria is associated with thyroid disease should be disregarded? Is it not rather our duty to investigate and study this type of borderline case more closely—to observe them for a decade or two—before we make any final statement regarding them? Even though the etiology of the metabolic disorder may be somewhat different in cases of hyperthyroidism than in cases of uncomplicated diabetes, we do know that many of these cases in the former group become frankly diabetic later. Does diabetes develop because the carbohydrate metabolism was "different," or because the insulogenic supply has been steadily decreasing? *A steadily decreasing insulogenic supply is diabetes,* whether one recognizes it in its earliest stages or only after the islands of Langerhans have become exhausted and frank or total diabetes has developed.

Effect of Thyroidectomy on Carbohydrate Tolerance. We have already offered evidence that in a considerable percentage of cases, feeding with thyroid extract, as well as hyperthyroidism, increases the blood sugar content, and if carried far enough, in some cases induces a functional state of diabetes. One can

observe this in any group of clinical cases in which the lagging carbohydrate tolerance varies from a very slight degree to a severe stage of diabetes. In some of the latter cases the diabetes will have passed beyond the functional stage, so that the changes in the islands of Langerhans are no longer reversible, and the insulogenic apparatus will have become permanently damaged.

If artificially induced or clinical hyperthyroidism produces the above picture, then one naturally inquires whether or not the elimination of the thyroid in such cases will increase the carbohydrate tolerance.

Friedman and Gottesman (77) report some interesting experiments in thyroidectomy and ligations of the thyroid arteries which were performed in depancreatized dogs, the protocols of which I offer as follows:

DOG NO. 100—WEIGHT 14 KGM.

Date, 1921		Urine Sugar
Jan. 12	Partial pancreatectomy	2-3% to Jan. 19
19	Both inferior thyroid arteries ligated	Glycosuria continued until Jan. 26
26	Complete thyroidectomy (sparing parathyroids)	Negative
Feb. 5	Blood sugar, 95 mgm. per 100 cc.; 3.4 grams pancreatic tissue removed	Negative
9	Blood sugar, 86 mgm. per 100 cc.; 150 grams glucose by stomach tube	Negative
May 9	Blood sugar, 66 mgm. per 100 cc.; rest of the pancreas removed (10 grams)	Negative
14	Wound opened—dog died. Autopsy showed complete absence of pancreas. Weight, 15.9 kg.	

DOG NO. 106—WEIGHT 7.52 KGM.

		Urine Sugar
Mar. 2	Complete pancreatectomy (18.2 grams)	
3		Plus (5-6%)
5	Superior and inferior thyroid arteries ligated	Present in decreasing amounts until March 8.
8		Negative until March 19, when distemper developed and dog died

2 Blood sugar, 76 mgm. per 100 cc.
4 Blood sugar, 250 mgm. per 100 cc.
5 Blood sugar, 192 mgm. per 100 cc.
6 Blood sugar, 90 mgm. per 100 cc.
7 Blood sugar, 50 mgm. per 100 cc.

Autopsy revealed complete absence of pancreas.

Thus, according to the findings of these authors, in dogs the diabetes which results from complete pancreatectomy may be rendered less severe by ligation of all the vessels of the thyroid gland and glycosuria can be caused to disappear by the subsequent thyroidectomy.

Janney and Isaacson (20) studied the effect of thyroidectomy on the carbohydrate tolerance of dogs by means of glucose tolerance curves. Some of their results are given in Figure XIX. The significant point demonstrated by these curves is that even though each was normal before thyroidectomy, after thyroidectomy the glucose tolerance was still further increased, a fact which suggests that the thyroid gland exerts an inhibitory action on the insulogenic function.

Holman (78) published a report of three cases of hyperthyroidism in which operations had been performed. This report is of special interest because during a very severe and alarming attack of postoperative hyperthyroidism in one of the patients the blood sugar was found to be 48 mgm. per 100 cc. This patient responded well to the administration of glucose. The other two patients did not have a severe reaction to the operation, and both showed a rise of blood sugar with the subsequent return to a slightly subnormal level 24 hours later.

Lund and Richardson (10) studied the blood sugar after operations on the thyroid gland in an attempt to discover whether or not hypoglycemia developed after the operation. Nitrous oxid-oxygen anesthesia was used, the duration of the operations being from 15 minutes to one hour. They found a rise in blood sugar in all operations on the thyroid gland in cases of hyperthyroidism similar to that in all other cases. They did not find hypoglycemia in any case.

My observations of the effects on the blood sugar of various operations are summarized in Table X and Figure XX.

Rohdenburg (3) reports the case of a boy 18 years of age in whom hyperthyroidism developed as a result of the administration of thyroid extract. The patient was kept in bed for four months without any improvement. A partial thyroidectomy was therefore performed, and six months later the urine was sugar-free, even after the ingestion of large amounts of carbohydrate.

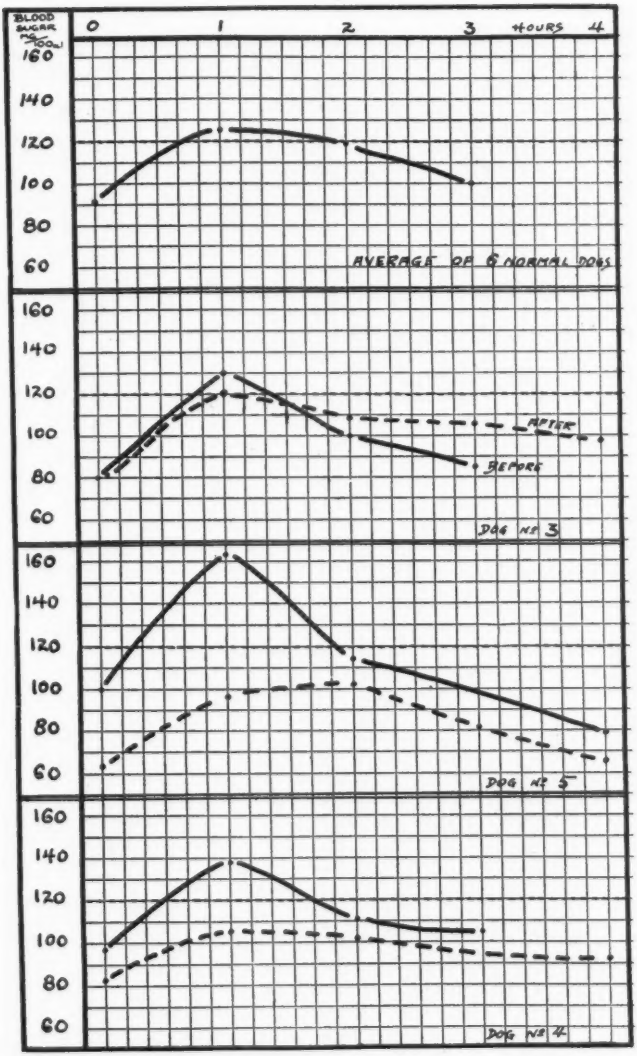

Figure XIX. Charts showing curves plotted from the findings of Janney and Isaacson in their investigations of the carbohydrate tolerance of dogs before and after thyroidectomy. In the first chart is given the average curve of six normal dogs; in the second, third and fourth, the curves in the case of individual dogs before thyroidectomy (the heavy line) and after thyroidectomy (the broken line).

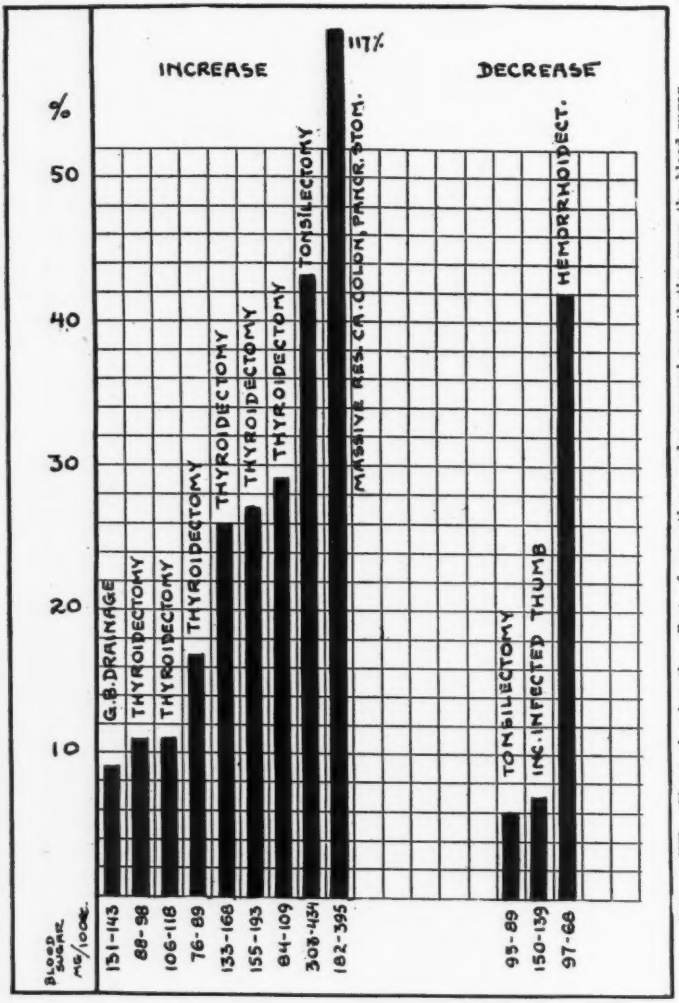

Figure XX. Chart showing the effect of operations under general anesthetics upon the blood sugar.

Rohdenburg reports also the case of a woman, 53 years of age, in whom a partial thyroidectomy had been performed for exophthalmic goiter. Several years later glycosuria developed; more of the thyroid gland was removed and the glycosuria disappeared. (Figure XXI.)

On the other hand, Fitz (51) states that partial thyroidectomy has no curative effect on diabetes.

TABLE X

THE EFFECT OF OPERATIONS PERFORMED UNDER GENERAL ANESTHETICS ON BLOOD SUGAR

Operation	Blood Sugar Before Operation	Blood Sugar After Operation	Percent of Increase	Percent of Decrease
Massive resection for carcinoma of pancreas, colon, stomach	182	395	117	....
Gall bladder drainage	131	143	9	....
Lobectomy	78	147	89	....
Thyroidectomy	88	98	11	....
Thyroidectomy	84	109	29	....
Thyroidectomy	106	118	11	....
Thyroidectomy	133	168	26	....
Thyroidectomy	155	193	27	....
Thyroidectomy	76	89	17	....
Tonsillectomy	303	434	43	....
Tonsillectomy	95	89	....	6
Hemorrhoidectomy	97	68	....	42
Incision of infected thumb	150	139	....	7

In my own series I need only to call attention to the following cases:

			Before Thyroidectomy	After Thyroidectomy	
Case No.	Sex	Age	B. M. R. plus %	B. M. R. plus %	Glucose Tolerance
109,856	M	34	21	7	improved
164,227	F	28	25	12	improved
160,342	F	60	41	..	improved
178,992	F	39	81	6	slightly worse

Thus of four cases in which I had the opportunity to recheck the glucose tolerance after thyroidectomy, marked improvement was shown in three and in one there was a slight retrogression. In the last case, however, a period of less than two months has passed since the operation, so that the result cannot yet be considered to be conclusive. The history in this final case is as follows:

Case V (178,992): A woman, 39 years of age, was first seen on February 8, 1927. She had lost 50 pounds in weight in less than a year. For seven months she had been very nervous, had had a rapid heart, had perspired and had noted an increasing lack of energy and increasing irritability. She had had an enlargement of the thyroid

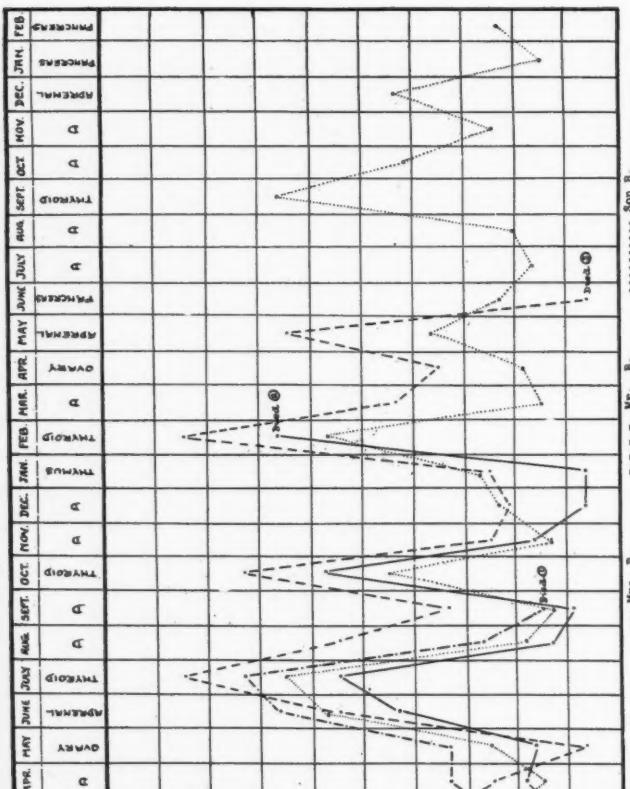
MEDICATION
MAR. APR. MAY JUNE JULY AUG. SEPT. OCT. NOV. DEC. JAN. FEB. MAR. APR. MAY JUNE JULY AUG. SEPT. OCT. NOV. DEC. JAN. FEB.
THYROID
OVARY
ADRENAL
PANCREAS
THYMUS
Sugar %
Mrs. A.
Mrs. B.
Mr. B.
Son B.
D-DIET RESTRICTED: SUGAR % IS BASED ON AVERAGE OF 4 DETERMINATIONS. 1 DIABETIC COMA. 2 SEPSIS, CARBUNCLE.
3 SUICIDE. (AFTER ROSENBURG)

Figure XXI. Chart showing the effect of adm inistration of thyroid gland substance upon glycosuria in four cases. (After Roldenburg.)

gland for 15 years. Nearly a year before she had had an attack of influenza and had not been well since that time. When I first saw her, her weight was about normal, but a year before she had been very much overweight (52 per cent). Her pulse rate was 144, blood pressure, 185/48. The fasting blood sugar was 161 mgm. per cc., and she had glycosuria—1.7 per cent. The basal metabolic rate was plus 81 per cent. Two glucose tolerance tests, one made before and one two months after thyroidectomy, have already been shown in Figure IX. During her stay in the hospital the fasting blood sugar was consistently normal and she received no insulin. It may be noted from this chart that while the second tolerance test showed a somewhat more prolonged hyperglycemia than that shown in the first test, yet the sugar output in the second test is much less than in the first, viz., only 0.15 gram, as compared with 5.46 grams. One wonders whether the renal threshold has changed or whether the permeability of the renal filter increased during the active stage of hyperthyroidism. The tests are but two months apart. Clinically the patient is well.

The Effect of Anesthesia on Blood Sugar. The effects of surgical operations on the blood sugar have been studied by Dewes (79) and by Epstein and Aschner (80). They found that hyperglycemia was produced by surgical anesthesia if the procedure was serious or prolonged. Epstein and Aschner found no change in the blood sugar in four minor operations done under local anesthesia. Five cases in which nitrous oxid-oxygen anesthesia was used showed an increase of blood sugar of from 10 to 30 mgm. per 100 cc. In sixty cases in which ether anesthesia was used there was a marked rise in the blood sugar—of over 100 mgm. per 100 cc., in some cases; a slighter rise was shown in some cases; and none at all in only three.

Insulin Treatment of Hyperthyroidism. During the past two or three years reports regarding the treatment of hyperthyroidism with insulin have appeared in the literature. With the advent of insulin it seemed logical to use it in the treatment of those cases of hyperthyroidism in which glycosuria and hyperglycemia were present. Much to the surprise of many of these reporters, however, in some cases not only were the symptoms of diabetes improved but the hyperthyroidism itself was either lessened in degree or even disappeared.

Thus Charvat (81) describes the case of a woman, 25 years of age, who had experienced a sudden onset of severe hyperthyroidism in 1921, the basal metabolic rate at that time being

plus 26 per cent. In 1925 the classical symptoms of diabetes appeared—glycosuria, 6 per cent and blood sugar, 340 mgm. per 100 cc. A glucose tolerance test with 50 grams of glucose gave the following findings:

		Periods after ingestion of glucose		
	Fasting	½ hour	1 hour	2 hours
Blood sugar..... Mgm. per 100 cc.	340	450	490	450

The patient excreted from 40 to 60 grams of sugar in 24 hours. For four months she was on a reduced diet and received insulin twice a day, without much effect on the symptoms of

TABLE XI

RESULTS OF TREATMENT OF HYPERTHYROIDISM WITH INSULIN

Author	Number of Cases	Improved	Worse	No Change
Castex	18	4	3	11
Charvat	1	..	..	..
Charvat	5	3	..	2
Charvat	5	5	..	..
John	2	1	..	1
Lawrence	4	3	..	1
Merklen	1	1	..	..
Puchulu	1	..	..	..
Senga	3	3	..	..
Thomson	1	1	..	..

diabetes, excepting that she excreted less than ten grams of sugar daily and the acetone in the urine disappeared, although the glycemia remained at about 300 mgm. per 100 cc. While the insulin seemed to have no effect on the diabetes, the hyperthyroidism improved markedly; the exophthalmos almost completely disappeared; the patient became quiet, slept well, and gained 8 kgm. in weight in ten weeks, the tremor of the fingers disappeared, and even the goiter became smaller by 2.5 cm. In the third month of this treatment the goiter had decreased still more; the basal metabolic rate was only plus eight per cent, the pulse rate 80, and all symptoms of hyperthyroidism had disappeared. Although the hyperthyroidism was cured, in February, 1926, the patient went into diabetic coma and died. Charvat thinks that insulin has some direct action—either primary or secondary—on the thyroid aside from its influence on the carbohydrate tolerance.

In 1925 Charvat (82) reported five cases of hyperthyroidism which had been treated with insulin. In two of these the

basal metabolic rates were plus 45 and plus 30 per cent, respectively. One of these patients left the clinic early, so that only a slight improvement was observed. The other patient remained for four weeks, during which time she gained seven kgm. in weight; the pulse rate was reduced from 100 to 76; the exophthalmos decreased; and although there was no change in the size of the gland, subjectively the patient felt well. In the case of another patient who had had a postoperative recurrence of hyperthyroidism, after ten days of treatment with insulin the pulse rate was reduced from 160 to 80; it then increased again to 100, where it remained. There was no change in weight, but the symptoms were markedly relieved. In another case in which hyperthyroidism had been induced by the use of iodin, treatment with insulin for four days produced no effect. In the fifth case the pulse rate fell from 110 to 90 within a few days and subjectively the patient felt well.

In this publication Charvat makes the following statement:

"If we summarize our results, we can say that we have obtained splendid results in several cases, but our desire to find in insulin a specific anti-Basedowian medicament was not fulfilled. In all cases we were able to restore, at least partly, the patient's condition, as was evidenced by a more or less marked increase in weight; but at the same time, in all the cases which we observed we had the impression that primarily the insulin did not directly affect the function of the thyroid itself, but rather the metabolism of the peripheral cells, into which the insulin penetrated as a nonspecific energy-sparer and fat depositor." In other words, "we felt that the patients who were emaciated and were standing their Basedowian disease poorly were transformed into fatter, more comfortable Basedowians, who were, however, in substance, still Basedowians."

Puchulu (83) mentions the favorable effects of insulin in cases of hyperthyroidism.

Senga (84) reports three cases of hyperthyroidism in which insulin was employed with good results, the basal rate having been diminished, the body weight increased, and the general nervous condition and the tremor having subsided, though the gland had diminished but slightly in size.

Castex *et al.* (85) used insulin—20 units daily for from 10 to 20 days—in the treatment of 18 patients: (1) with exophthalmic goiter; (2) with simple goiter associated with the meno-

pause, these cases showing symptoms of hyperthyroidism; and (3) with thyroid insufficiency. In three of these cases the basal metabolic rate was increased, in three it was lowered, in one instance it was lowered to normal.

Lawrence (86) tried to eliminate all extraneous influences in four cases of well advanced hyperthyroidism, and did not begin to use insulin until mental and bodily calm was established. The first case was that of a woman, 23 years of age, in whom the hyperthyroidism was so severe that the surgeon considered that operation was contraindicated. The patient was kept quiet for seven weeks, without insulin, but her condition became worse, and she was losing weight. During this time she received sterile injections of water. Injections of insulin were then started without the patient's knowledge. Four days later she announced that her neck felt easier; after ten weeks, during which she received 80 units of insulin daily, she had gained 34 pounds, the thyroid had become reduced in size, her pulse rate had fallen from 114 to 78, and the basal rate from plus 58 per cent to plus 13 per cent. She was discharged from the hospital apparently well. The second case reported by Lawrence was also that of a woman, 28 years of age. In eight weeks she gained 24 pounds and was discharged practically well. The third patient, a woman, 50 years of age, who had an adenoma of the thyroid, reacted to the treatment with insulin only by a slight increase in weight. The fourth case was that of a woman, 47 years of age, with a nodular struma. This patient did not react to the insulin.

Merklen *et al.* (87) report the case of a woman with a typical exophthalmic goiter, whose first attack of hyperthyroidism developed post-partum. Her condition improved after the use of hematothyroidin. A second attack of hyperthyroidism was followed by diabetes, as shown by glycosuria and a blood sugar level of 280 mgm. per 100 cc. Insulin was given in doses of 20 units per day; both the diabetes and the hyperthyroidism improved.

Thomson (88) reports the case of a middle-aged woman who, three weeks after the onset of exophthalmic goiter, was almost maniacal. She vomited constantly for four days, had a pulse rate of 150, and had auricular fibrillation. The condition seemed desperate, and after two days all other treatment

was stopped and the administration of insulin was started with doses of five units each, three times a day, together with frequent sweetened drinks. There was no glycosuria, but the mouth of the patient was parched, and she complained of thirst. Within a few hours definite improvement was noted, and this continued. The dose of insulin was increased to 30 units daily, in three doses of 5, 20, and 5 units, respectively. Hypoglycemia developed and the insulin was changed to two daily doses of 5 units each. The vomiting stopped, abdominal distress disappeared, and mentally the patient became more calm. These results are the more remarkable since the patient was apparently in a dying condition when she was brought to the hospital.

Bodansky (89) and Ducheneau (90) found that thyroidectomy enhanced the activity of insulin. Burn and Marks (91) showed that thyroidectomized rabbits were three to nine times more sensitive to insulin after the operation than before.

My own experience with the use of insulin in cases of hyperthyroidism is unlike that of the authors cited above. All cases in which the carbohydrate metabolism is slightly disturbed respond promptly to insulin, as one would expect. Small doses of insulin in addition to a regulated diet, together with the administration of iodin and rest in bed, do greatly improve the condition of these patients. The body is thus given an opportunity to store glycogen in the liver, which is a cardinal principle in the treatment of all cases of hyperthyroidism, whether they are diabetic or non-diabetic. In one severe case in which diabetes had followed the onset of hyperthyroidism in a young man, whose basal metabolic rate was plus 89 per cent, the patient did not respond in any way to insulin as far as the hyperthyroidism was concerned, and even after a double lobectomy his basal rate continued to be as high as plus 71 per cent. In this case a small nodule of thyroid tissue, one by two cm. in size, had been left; after this was removed, the basal metabolic rate became normal, and the myocarditis and diabetic condition were improved.

One patient, however, was distinctly benefited by the use of insulin and all the symptoms of hyperthyroidism subsided, so that it has not been necessary to operate. From a condition of serious invalidism this patient has progressed so that at the present time she is leading an active life. Insulin has been

discontinued now for nearly a year, and her blood sugar is remaining normal on a fairly liberal diet. This case seems of sufficient interest to justify the following detailed report:

Case VI (167,806): The patient was a married woman, 61 years of age. The family history contained no pertinent information. The patient had had mumps and whooping cough in childhood; measles and pneumonia at the age of 18 years; tonsillitis, rheumatism, and pleurisy later in life; typhoid fever at the age of 40. There was no history of jaundice or of gall-bladder disease. An ovarian tumor had been removed in 1907 and a herniotomy had been performed in 1910. The patient had three living and healthy children.

Diabetes had been definitely discovered a few days before I first saw her, on June 5, 1926, although she had had the classical symptoms for several months. She weighed 147 pounds, but her usual previous weight had been 187 pounds (the normal weight for her height, 5 feet 4 inches, would be 131 pounds). Two weeks before she had had a vomiting spell which lasted for four hours. She said that a diagnosis of gastric ulcer had been made several years before, and during the preceding five years she had had four or five hemorrhages from the stomach. She had recently had dimness of vision. She had nocturia, being obliged to urinate twice each night.

Physical examination showed a well nourished woman with no pallor. Her blood pressure was 140/76. The pupils were equal, reacting well to light and accommodation. The ears were normal. There was no adenopathy. A moderate sized adenoma of the thyroid was present. The lungs were clear. The heart was not enlarged; the rate was 90; regular, no murmurs or irregularity were detected. The abdominal wall was lax. She had a ventral hernia. The spleen was greatly enlarged, firm and smooth, extending about six inches below the costal margin. There was no enlargement of the liver.

The Wassermann test was negative. The blood clotting time was five minutes. There were no bile pigments in the plasma. The serum bilirubin was 0.6 mgm. per 100 cc. There were 170,000 blood platelets per cu. mm. The blood clot retracted in 1½ minutes. The blood sugar was 352 mgm. per 100 cc. Urine sugar was one plus. There was no albumin. X-ray examination of the gastro-intestinal tract gave normal findings.

The diagnosis was: Diabetes mellitus, Banti's disease, hyperthyroidism and ventral hernia.

Insulin and a diabetic regimen were prescribed and on August 16, 1926, a little more than two months later, the condition of the patient had improved greatly. The nervousness which the hyperthyroidism was causing had practically entirely disappeared, she looked well and said that she felt well. At that time she was taking ten units of insulin per day and the diabetic condition was evidently under control. There was no change in the size of the spleen, which

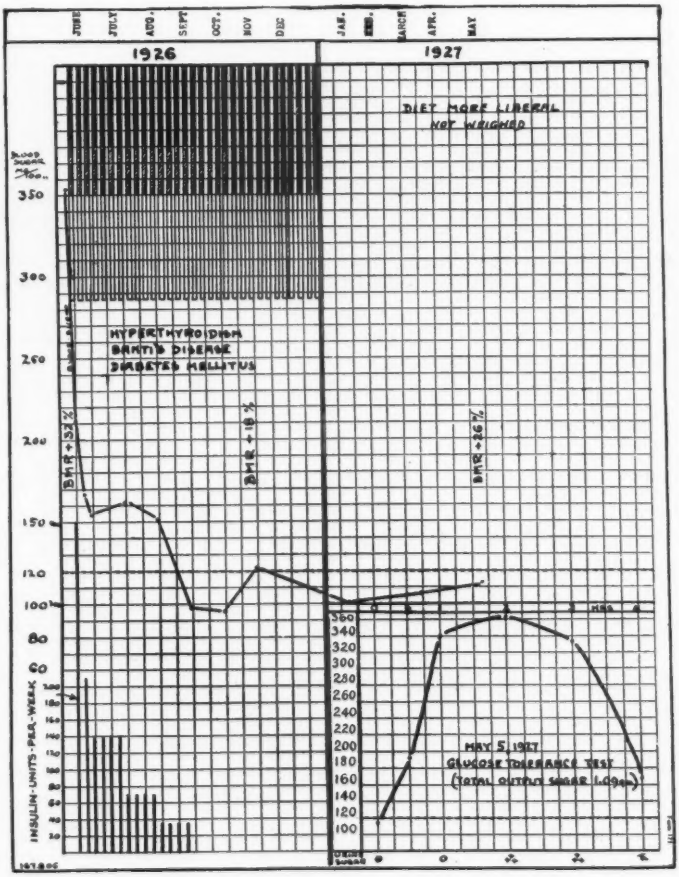

Figure XXII. Chart showing the course of a patient with hyperthyroidism, diabetes and Banti's disease, who was under treatment with insulin (Case VI).

could easily be felt from four to five inches below the costal margin.

One month later, on September 16, 1926, the patient was feeling "fine," was working, attending social functions and still steadily improving. Her general condition was normal excepting for the sensation of pressure in the abdomen from the enlarged spleen.

Figure XXII is a graphic representation of the data in this case. It will be seen from this that the patient's fasting blood sugar remained normal and she remained sugar-free until May, 1927, on a fairly liberal diet, which was only estimated, not weighed. Except for exophthalmos, which had not receded, she had no symptoms of hyperthyroidism, and it looked as though the diabetic condition might also have subsided. In order to test the latter condition a glucose tolerance test was made on May 5, the results of which are shown in the lower right corner of Figure XXI. The curve indicates definitely a diabetic condition, showing that the diabetes is controlled but not eliminated. A basal metabolism estimation was also made, and this showed a rate of plus 26 per cent. Clinically, therefore, this patient is well, but from a laboratory standpoint she is still a diabetic with a high basal metabolic rate.

Postoperative Acidosis. Acidosis is a well recognized postoperative complication of thyroidectomy. The pulse rate in such cases is high and the patient becomes semicomatose or stuporous immediately after operation. Is the acidosis in these cases of the same type as diabetic acidosis? Diabetic acidosis is due to the inability of the organism to burn glucose, this in turn producing an incomplete combustion of fats with the resultant accumulation of ketone bodies in the blood stream (acetone-diacetic acid-beta oxybutyric acid) and consequent acidosis. In uncomplicated hyperthyroidism, however, there is no such inability to burn glucose, but there is rather an inability to store glycogen and a general increase of the metabolic processes, so that all available carbohydrate, including the glycogen reserve of the liver and muscles is utilized, with resultant *hypoglycemia.* Holman (84) cites a case of hyperthyroidism in which the basal metabolic rate was plus 29 and plus 35 per cent. After thyroidectomy, the pulse rate rose to between 180 and 250, immediately after operation, this very high rate lasting for 60 hours. Twenty-four hours after the operation the patient was in a semicomatose condition and her blood sugar at that time was found to be only 48 mgm. per 100 cc. Glucose solution—20 per cent—was administered, and immediately she became conscious, but six hours later she again went into a deep stupor. She was

again given glucose, and again immediately became conscious. It is clear that in this case the stupor was due to hypoglycemia, a condition similar to the hypoglycemia of an insulin reaction.

SUMMARY

A report is offered of a study of the carbohydrate metabolism in 92 personal cases, together with a discussion of the pertinent literature. The following conclusions are reached:

1. There is no glucose tolerance curve specific for hyperthyroidism. That is, a definitely diabetic type of curve may be present in a mild case of hyperthyroidism and a normal curve may be present in a very severe case of hyperthyroidism. While hyperthyroidism, like infection, obesity, overeating, etc., may make manifest the presence of a latent form of diabetes or may change this prediabetic condition into true diabetes, I believe that hyperthyroidism rarely induces a diabetic status in an individual in whom there is a normal insulogenic reserve. The change from a prediabetic to a diabetic status, which is sometimes associated with hyperthyroidism, I believe to be the result of the overeating, which, in turn, is due to the increased metabolism. The food which is usually craved and eaten by these patients is especially rich in carbohydrate, and thus an unusually heavy load is thrown on the islands of Langerhans. If this over-load continues over a long period of time it is logical to expect that the islands will become exhausted, with a resultant breaking down of the carbohydrate metabolism; the classical picture of diabetes will then be superimposed upon that of active hyperthyroidism.

2. Thyroidectomy lowers the total metabolism and in consequence improves the carbohydrate tolerance. In cases in which little or no improvement follows thyroidectomy this is due to the fact that lack of proper diabetic treatment or insufficient treatment has followed the operation.

3. If diabetes develops after a thyroidectomy, this is due either to other extraneous factors such as produce diabetes in other cases or to the fact that an insufficient amount of thyroid tissue has been removed. In the latter case, when more of the gland is removed, the diabetes is improved.

4. A number of authors, with whom I agree, believe that hyperthyroidism plays a fundamental etiologic rôle in the dis-

turbances of endocrine equilibrium which constitute the diabetic syndrome.

5. Glycosuria and hyperglycemia (either fasting or, more often, two and one-half hours after a meal) are not uncommonly present in hyperthyroidism. When found they should not be disregarded, but their significance and their relationship to the carbohydrate metabolism should be determined by appropriate tests.

6. I consider that the presence of hyperglycemia two and one-half or more hours after a meal is an expression of an insufficient insulogenic function. While I appreciate that other physiological factors are concerned, I consider that these are of secondary significance; and whatever academic interest they may have, they should not be allowed to interfere with the institution of the appropriate measures for the safety of the patient.

7. The intervention of the menopause in a case of hyperthyroidism may cause hypertrophy of the islands of Langerhans with the resultant cure of a coincident diabetes. This probably, however, is a rare occurrence, for but few cases are reported in the literature.

8. The glycogen depletion of hyperthyroidism increases the tendency to acidosis. This factor is aggravated in cases in which diabetes is present. The ingestion or the intravenous administration of glucose before or after operation, with or without insulin, according to the indication in the individual case, would seem to be a logical procedure. The factors which influence the glycogen depletion are probably the following:

(a) Toxic influences which directly affect the parenchyma of the liver cells.

(b) A high metabolic rate which causes increased consumption of carbohydrate and depletes the insulogenic stores, which in turn depletes the glycogen store in the liver. Such a depletion is also shown in uncomplicated cases of hyperthyroidism which do not show a high blood sugar.

9. Patients with hyperthyroidism in whom a frank diabetic condition of severe type is not present, but merely a mild degree of disturbance of the carbohydrate metabolism, I consider to be "functional" diabetics. Up to a certain point diabetes is a reversible process. These functional cases clear up

eventually after thyroidectomy or some other type of treatment, but without such treatment they do not clear up and frank diabetes develops unless the prediabetic or functional condition be extremely mild. For that reason I have emphasized the importance of taking cognizance of a delayed glucose tolerance curve in cases of hyperthyroidism. Some authors consider this hyperglycemic condition to be due to an over-production of sugar in hyperthyroidism, and offer as an explanation for this view the normal rise of the R. Q. curve after the ingestion of glucose. This is quite true up to a certain point. The increased demand for insulin is satisfied as long as the supply can cope with the demand. But when the supply of insulin is exhausted, even the R. Q. comes down to a diabetic level. For this reason the pancreas should be protected whenever a weakening of the carbohydrate metabolism is evident. Interesting as it may be scientifically, it is of little immediate consequence to determine *why* the liver of a patient with hyperthyroidism is glycogen-free or glycogen-poor. The important fact is that it *is* glycogen-free or glycogen-poor, and the medical problem is to restore the normal status of the liver.

10. The administration of thyroid preparations is not without danger. It may precipitate hyperthyroidism, and may even produce diabetes.

11. In my series of 100 glucose tolerance tests in 82 cases of hyperthyroidism and 10 cases of colloid goiter, fasting glycosuria was present in 19 cases and absent in 81 cases. Sixty-six per cent of the curves indicate an impaired tolerance, and 34 per cent indicate a normal tolerance. It must be remembered, however, that these glucose tolerance tests were not made in consecutive cases of hyperthyroidism but in picked cases; the tests were made because of the presence either of glycosuria or of hyperglycemia two and one-half or more hours after a meal. Moreover, 10 cases in this series were of colloid goiter without hyperthyroidism. Therefore these percentages do not represent an average incidence of impaired glucose tolerance in cases of hyperthyroidism, but rather the incidence in a selected group.

12. From the observations in these cases it would appear that the renal permeability is increased in the active stage of

hyperthyroidism. The renal threshold for glucose was below 120 in 35.6 per cent of the cases.

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PATHOLOGY OF GOITER

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Attempts have frequently been made to formulate a classification of goiters which should provide a separate group for all the various pathological and clinical entities. The more I study goiters the more I am convinced that the goiterous disease is a more or less continuous process, and the various pictures declare the state of development rather than a pathological or clinical entity. We should speak of the stages of goiters rather than of kinds. One does not have the proper mental equipment for the study of goiters unless he knows the life history of patients who run their course without treatment. Practicing in one community for a lifetime, I have been able to trace repeatedly the process from the adolescent colloid to the bossilated masses of middle life, and finally the cardiac decompensation and evidence of dysthyroidism. One of the chief difficulties lies in the proper interpretation of the clinical picture. The patients must be considered aside from the goiter in order that irrelevant symptoms may be properly classified. The condition of the patient following operation must be traced for an indefinite period. Indeed the study is not completed as long as the patient lives. It is only by keeping these facts in mind that one can predict from the clinical picture what the slide will show.

The simplest classification as heretofore published distinguishes two great classes of goiters. The colloid, characterized by the excessive collection of colloid with the subsequent development of accessory (possibly compensating) acini, resulting in a long line of various types of degeneration. This group is characterized by the excessive colloid content. In early life this appears as a more or less uniform enlargement, causing no considerable disturbance. In early maturity this gland becomes irregularly bossilated by the more rapid growth of certain areas. By successive remissions and exacerbations the development continues. Often the increased growth is associated with pregnancy or some other periodic disturbance. It is interesting to note in

this connection the comparative rarity of this type in the male. When this bossilated state is reached, the term adenoma has been applied. This is most unfortunate, for in no sense is the term "oma" applicable. The disturbance is in no wise tumerous, but always functional, and the nature of the functional disturbance can be read in the anatomical structure of the gland. There is everywhere evidence of failure and an effort to compensate for it.

In the other type there is a marked cellular proliferation, resulting in typical Graves' disease. The characteristic feature is marked cellular proliferation with or without actual papillary formation in patients who have eye signs. It is a mistake to assume that the whole gland is made up of this type of structure. As a matter of fact, those of us who have published such pictures have been obliged to search our slides to find such areas. The largest part of the slide is made up of far less active cellular proliferation. True, in a few the larger part of the gland is made up of papilla-bearing areas, but these are rare. In the great majority a part of the gland is made up of old colloid acini associated with the formation of new acini, with a greater or lesser number showing active cellular development, resulting in papillation.

The cause of the glandular increase is not known. Whether it ever is developed as a primary process or whether the cells are spurred to activity by a previous change, is not known. There is evidence that there are always previous changes. If so, this type may be but a type of the former. It is easier to conceive that some change in the colloid stimulated the cells to activity than that they just happened to develop. It is difficult to form an opinion, because the range of variation in the normal is little understood.

When a large number of goiters representing Graves' disease are studied, one finds the dividing line between the so-called toxic adenomas and the Graves' disease to be a narrow one. It represents an acute exacerbation, rather than a new or distinct process. Hence, instead of separating them from the old colloids, we contribute to clarity by considering them as a variation in the process. Hence, all goiters may well be considered as stages and variations of a single thyroid disease.

True enough, many cases of Graves' disease appear of sud-

den development in patients previously free from goiter. Much confusion has arisen because we have taken the patient's word as to the date of the appearance of a goiter. When a patient comes to us with a cancer of the breast the size of a walnut, and declares the tumor developed from a bump from a broom handle ten days previous, we are not misled. Yet when a patient comes to us and tells us that his goiter first developed a few weeks or months ago, we believe the statement. Yet on examining the gland in the laboratory we find old acini, newly developed acini, and vascular and tissue changes that must have required years to form. Many patients, of course, come with obvious goiters who never knew they were so afflicted. The patient's statement of the duration of a goiter is wholly valueless and must not be allowed to enter into the argument. A careful microscopic study of the gland, on the other hand, gives very accurate evidence. A superficial study is not sufficient. The changes in the acini and connective tissue must be studied by specific stains. Histo-chemistry must be brought to the aid of topographic pathology. In conformity with this conception, the following groups, therefore, are to be looked on as the various stages in the development of the goiterous disease, rather than separate types. We may mention them in the order of their occurrence.

Adolescent Stage.—This, as the name implies, is the goiter of early life. They are characterized by relatively large, elastic, often very soft, goiters, usually symmetrical in form. They usually do not markedly disturb the patient, but when nervous patients possess them toxicity may be simulated. The more I study patients with these early goiters, the more I am in doubt as to whether or not they ever are symptomless. The patient exhibits evidence of nervous hyperactivity and generally a pulse that is somewhat augmented. Even from the earliest beginning there are no innocent goiters.

Histologically, these glands show large acini filled with a homogeneous acidophilic colloid. Even in this early stage there is usually evidence of new gland formation in the interstitial cells or in the walls of the acini. A goiter made up wholly of large acini without any cellular activity is very rare. In the 1,000 glands on which this study is based there is not one example. True enough, areas large enough from which a photomicrograph

may be made are found, but when the whole slide is examined, or slides from various areas, cellular activity will most certainly be found in some parts of the gland.

As a corollary to this stage, it is necessary to consider the small, firm goiters which Goetsch and I have called interstitial goiters. There are found in girls and young women. The glands are small, symmetical, and usually firm to the touch. It is unfortunate that these have been classed with goiters for they are usually associated with dysmenorrhea and intermenstrual pains. If they were regarded as they should be, as pluriglandular affections, there would be a greater likelihood of properly interpretating the lower abdominal pain and help us to understand the nature of the mythical "chronic appendix."

Microscopically these glands show some colloid increase, but it is for the most part unchanged. The acinal epithelium is flat. The interstitial cells are prominent, reminding one of the appearance of thyroids in children. In these there is no new gland formation.

Colloid Stage (Innocent Colloid). The old long standing goiters develop irregularities so that the goiter becomes bossilated. This irregularity of form is brought about by the development of some lobules more rapidly than others. If one has a chance to observe a goiter over many years one can note from time to time the appearance of some new bossilations.

These bossilations owe their restriction to the fibrous tissue septae which characterize the normal gland. On section these bossilations are seen to be made up of many small lobuli, each representing a lobule in the normal gland.

Histologically one sees that the increase in size of the lobule is dependent on the development of small acini in the interstitial cells or within the walls of the old acini. The cells lining the old acini are seen to be flat endothelial-like, while those of the smaller ones are cuboid, suggesting that these small glands are carrying on the function and really constitute a compensatory hypertrophy. The source of the new acini is unquestionably the interstitial cells and likely, in part, the walls of the old acini.

It is by this process that the goiter becomes lobulated. The large lobuli are usually made up of many smaller ones. These

smaller lobuli may undergo changes, each for itself, giving to the section a mottled appearance.

During this development the patient is but little disturbed by the gland, yet if the symptoms are studied carefully periods of nervousness, loss of weight and rapid pulse will be discovered.

Chronic Toxic Stage (Toxic Adenoma). Sooner or later the patient is compelled to recognize definite disturbance. When this stage is reached there may be notable change in the size or outline of the gland, or in its consistency. True, patients sometimes state that the glands have become larger recently. As a rule their complaints are not of any physical change of the gland but of general disturbance. They become nervous, lose weight, become sleepless, and have a rapid pulse, and the like.

Histologically, in the majority there is most often sign of cellular activity either in the newly formed acini or in the epithelial lining of the old acini. The cells of the acini are cuboid, seldom columnar. Many new acini are in evidence. Various areas of the gland nearly always still show the structure of the old colloid stages. It is only in certain areas that the cellular increase is marked. The goiter now has become a toxic adenoma, according to the generally accepted terminology.

In many of these there is no evidence of cellular activity but everywhere there is evidence of degeneration. This is notable particularly in those cases going on to a rapid death. What part degenerative processes play in the less active cases is difficult to say.

Acute Toxic Stage (Graves' Disease). These may begin rapidly in patients who did not know that they had previously had a goiter; nor does the surgeon, in many instances, until he has examined the gland in the laboratory; or the condition may be implanted on a known preexisting goiter. The clinical symptoms are characterized by greater intensity as well as more rapid onset. It is a matter of degree rather than of kind. If implanted on a known preexisting goiter we have the so-called Basedowified colloid, which, in the light of the present study, seems an inspired designation.

In the more intense types eye signs are present. In many patients one can predict that eye signs will develop. In general

the presence of eye signs indicates the severer types, but equally severe types are found without the presence of the eye signs.

Histologically this type is characterized by active epithelial proliferation. If one is to employ an oncological cognomen one could with good grace call these "adenomas," for in an active gland the imitation to a malignant adenoma is very close. The glands develop by forming new glands in the interstitial cells as well as the papillary projection of cells into the lumen of the acini. The cells are cuboid or cylindrical. In the very active cases the latter predominate.

In small glands the greater part may be made up of such active proliferating glands. In those developing on old colloids only certain areas are so affected. Since most of the acutely toxic glands are found in early life the glands are usually small and the evidence of old colloid change is not so prominent. It takes many years to produce an old lobulated colloid goiter. In the small glands, however, many acini are found which contain a vacuolated colloid. Recently this is ascribed to the use of Lugol's solution, notwithstanding the fact that the same picture was present before Lugol's was used. In no case in my experience is there evidence that a Graves' disease developed in a normal gland. It would appear warranted in assuming that the changes in the thyroid gland preceding the development of toxic symptoms is one of degree instead of one of kind.

The conception of all goiterous diseases as stages of one process facilitates the understanding that there are no innocent goiters and that all, sooner or later, will lead to toxic states jeopardizing the life of the patient.

SUMMARY

From a study of 1000 cases personally observed the following conclusions are drawn:

1. Goiters without evidence of new gland formation are rare.

2. The development of new acini is more or less progressive.

3. The exacerbation of this development comes sooner or later and is characterized by greater activity of the epithelium or some associated degeneration.

4. When the gland proliferation is very active the clinical symptoms are more pronounced but not essentially different in kind.

5. In view of the obvious shading of the various clinical and pathological pictures into one another it seems it would clarify our clinical conception, and lessen the burden of the pathologists, by considering the whole as one disease of which we can speak of stages, rather than of kinds.

ADDISON'S DISEASE WITHOUT PIGMENTATION: REPORT OF A CASE*

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Pigmentation is so constant and striking in Addison's disease that in its absence an unconfirmed clinical diagnosis will be accepted with reservations. Yet it is definitely known that Addison's disease does occur without pigmentation. The diagnosis can be made clinically and at times with considerable certainty as indicated in the following case:

REPORT OF CASE

A man, aged forty-five, born of Scotch parentage in the British West Indies, a hardware merchant in northwestern Canada, came to the Clinic, June 8, 1927, complaining of weakness, dizziness, dyspnea, and palpitation of ten months' duration. The symptoms during the last two months had become progressively more marked. His father died from typhoid fever, and his mother from an unknown cause at the age of fifty. The patient had been married seventeen years and had three children living; one child died in infancy from congenital lymphatic cysts. Aside from typhoid fever at ten and occasional colds, he had never been ill. He was said to have been a man of unusual energy.

In the summer of 1926, while working in his garden, he began to realize that he was weak and not in good physical condition. Backache developed readily and he said that it was a relief to sit down and rest. In October, 1926, what appeared to be neuritis of the brachial plexus developed and was treated by heat, massage and electricity. He did not improve satisfactorily and went to Honolulu for the winter, resting two months, with some benefit. He returned to work in April, but within a short time pain developed in the chest which incapacitated him for a week, and pleurisy was diagnosed. The following week he had two devitalized teeth removed, and subsequently an acute cold persisted for a week. During April he had "weak spells" which necessitated a two weeks' rest. Two weeks later, while walking home

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from his work, a distance of a mile, he felt faint, or "all in." He called his physician, who again advised rest. Subsequently he had not been able to stand any length of time without feeling faint and weak. He felt dizzy on changing from the recumbent to the upright position. This was accompanied by a peculiar feeling of sickness in the pit of the stomach. Shortness of breath and palpitation on exertion were noted. His appetite was fair, but the effort of eating tired him. There was considerable abdominal distress, with belching and flatulence after eating. He had lost 15 pounds in weight in two months. The joints became sore on walking. Some residue of neuritis in the right arm still persisted and he was restless and slept poorly.

Physical examination revealed a weak, restless man, 5 feet 10.5 inches tall, weighing 140 pounds. The tonsils were small and buried. The heart sounds were distant and slightly irregular. The lungs were normal except for slight dullness and slightly decreased fremitus anteriorly and posteriorly over the left upper lobe. Roentgen-ray examination of the chest disclosed no abnormal condition. The abdomen was normal to palpation. The pulse was 92, temperature 97, systolic blood pressure 86, and diastolic 64. The condition was regarded as probable postinfectious exhaustion. The low blood pressure and the dizziness on standing suggested postural syncope or postural hypotension. Because of the extreme weakness, further examination in the Clinic was deemed unadvisable and he was admitted to the hospital for further study.

In the hospital, ephedrine, which has been found of decided value in certain cases of postural hypotension, was tried, but without favorable results. The heart sounds were poor in quality, extremely faint and heard better with the naked ear than with the stethoscope. The blood pressure continued to be about 80 systolic, and 50 diastolic, until the sixth day, when it reached the low level of 68 systolic and 48 diastolic. Addison's disease was suggested and a most careful search made of the skin and mucous membrane for evidence of pigmentation. The man's complexion was decidedly ruddy and showed no evidence of tanning or darkening of the skin, even in the exposed areas. There was an occasional dark freckle over the face and neck, but there was not the slightest trace of pigmentation of the mucous membranes. Despite the absence of pigmentation and the ruddy complexion, a diagnosis of Addison's disease without pigmentation was made from the clinical picture.

An observation of unusual interest was the depressed, canal-like groove of the frontal vein, descending over the forehead. This venous canal could be filled when the head was in the dependent position, but was replaced by an excavated depression or groove with the patient in a normal position, lying, sitting or standing.

The patient was placed on a mild Muirhead regimen on which he did poorly. At the end of a week this was discontinued, because it was felt that he evidenced an actual intolerance to adrenal products.

All drugs, aside from hypnotics, such as allonal and phenobarbital (luminal), which were required for sleep, were discarded. Blood pressure continued to decrease and clinical improvement was lacking. A second trial of the Muirhead treatment was made, using very small doses of epinephrin, but, aside from slight increase in blood pressure, no improvement was manifested.

Abnormal changes in blood pressure relative to posture were exhibited by this patient. When his position was passively varied while lying on an adjustable table, each fractional raising of the head from 45 degrees below horizontal to the perpendicular upright position resulted in a step-like fall of the blood pressure from 80 systolic and 60 diastolic (head down) to 60 systolic and 54 diastolic (head upright). Mortensen's* series of ninety normal women exhibited an average mean fall in blood pressure of 4 mm. systolic and an average mean rise of 8 mm. diastolic during essentially the same passive changes in posture. The pulse rate of the patient increased from 72 (horizontal) to 90 when passively changed to the upright posture, which is a considerably higher rise than the average mean rise of 10 pulse beats a minute which Mortensen's ninety normal women exhibited. The same observations of pulse and blood pressure, made in a typical case of postural hypotension with syncope, revealed an abnormal, step-like fall of blood pressure from 128 systolic and 98 diastolic (horizontal) to 56 systolic and 40 diastolic (upright), while the pulse rate remained unchanged.

The patient became progressively weaker, irritable and restless. Voluntary lifting of his head or extremities from the bed surface soon required visible effort. All food was distasteful and seemed to disagree. A sighing sort of respiration developed and became more marked, a tracing indicating it as a true Biot type.† The urinary output began to decrease at the end of the first week, dropping from 2400 cc. to 800-1000 cc. The phenolsulphonephthalein output decreased from 60 per cent to 30 per cent. The blood urea mounted from normal until it reached the level of 89 mgm. for each 100 cc., while the blood sugar remained at from 0.092 to 0.12 per cent. There was no cytologic change in the blood. The basal metabolic rate was —9 and gastric analysis showed total acidity, 44, and free hydrochloric acid, 32. At this time the patient was so weak that his voice became husky and muffled, with slurring of the syllables. Decubitus appeared in the left ear. He was clear mentally except for slight fogging just before death. On the last day he became somewhat cyanotic. He was given glucose solution intravenously, a small transfusion, and oxygen from an oxygen tent. Under the latter treatment he breathed with greater comfort and slept. Respiration decreased to 6 and 8 a minute, and coma and death followed.

Necropsy was refused, but a limited examination for the purpose of determining the presence or absence of tuberculosis was permitted.

*Mortensen, M. A.: Blood pressure reactions to passive postural changes. Am. J. M. Sc., 1923, 165, 667-675.

†This type of respiration has been noted previously by one of us (Rowntree).

The pathologist's report was tuberculosis of the suprarenals, Addison's disease, healed tuberculosis of the left lung, hilus nodes and pleuras; emaciation was graded 2.

This patient, therefore, represents a case of Addison's disease resulting from tuberculosis of the suprarenals in which the clinical course was typical in every respect, except for the absence of pigmentation. The course was rapidly and continuously downward. The patient was not benefited by epinephrin and adrenal cortex, but appeared, in fact, intolerant to them. The diagnosis was made clinically and was confirmed by pathologic examination. Such cases as this are rare.* This represents the first instance of "Addison's disease without pigmentation" confirmed pathologically in the Mayo Clinic, although more than seventy cases of Addison's disease have been observed and studied.

*A case was observed previously in the Clinic in which, in the absence of pigmentation, the diagnosis of Addison's disease was made clinically. Since necropsy was refused, confirmation was not possible. In that instance, also, the downward course was progressive and considerably more rapid than is usual in Addison's disease.

A CASE OF PHYSIOLOGICAL CASTRATION IN THE FOWL

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Much of the knowledge of the relations which the functioning reproductive glands bear to somatic development has been gained from operative experiments. However, in some cases, abnormal individuals have been observed which have provided evidence concerning these relations. There came to our notice some time ago a case in the latter group. A Plymouth Rock cock had been purchased from a high grade pen for breeding purposes. To all appearances the bird was a normal young male but before he had reached the breeding age he came gradually to resemble a capon. Especially were the development of his comb and wattles, and the general shape and appearance of the body characteristic of a castrated bird.

Unfortunately the bird died in the pen several hours before we had the opportunity to examine him. No notes were available concerning his behavior except that we were told by the owner that he acted like a capon and was driven about by the other birds of both sexes.

Post-mortem examination gave evidence that the bird had died of a disease which had been progressing for some time. The whole body was emaciated and there were no fat deposits such as are characteristic of healthy birds. Many of the organs seemed to be more or less involved, as several were found with small caseous nodules varying in size up to 7 or 8 mm. in diameter. Microscopic examination failed to give evidence of bacterial invasion. In some cases these nodules seemed to be characterized by increased amount of connective tissue and were richly infiltrated with blood.

The gonads were the subject of special attention. They were much smaller than those of a healthy bird, the left measuring 14x5 mm., the right 13x6 mm. A microscopical examination also showed the testes to be very abnormal. Spermatogenesis was practically lacking. The tubules in the peripheral one-third

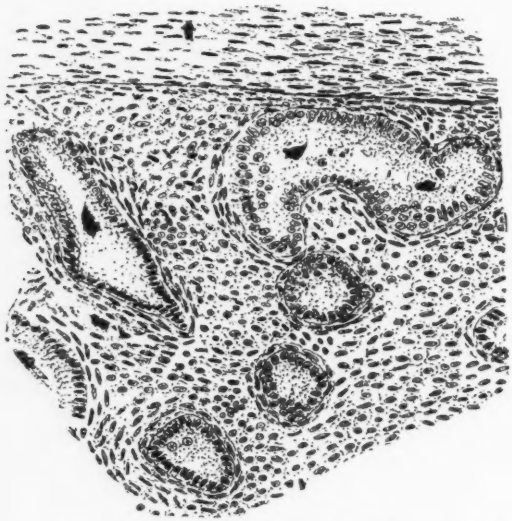

Figure A. Camera lucida drawing of portion of peripheral region of testis.

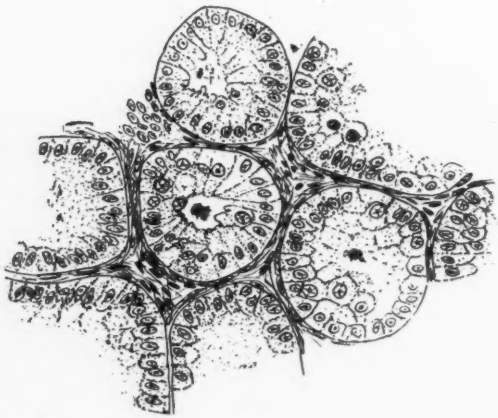

Figure B. Camera lucida drawing of portion of central region of testis. Compare with Figure A.

of the radius of the testes were markedly degenerated and somewhat wrinkled in contour, while the inter-tubular spaces were wide and more or less filled with spongy connective tissue (Figure A). The large number of red blood corpuscles indicated an inflamation. Toward the center of the cross-section the tissues appeared less abnormal. The tubules were close together, rounded, with smooth contours, and the amount of inter-tubular substance, both connective tissue and blood cells, appeared to be much less than in the peripheral layer (Figure B). In neither zone were found typical "interstitial" or "luteal" cells. The peripheral zone of degenerated and wrinkled tubules seemed to be proportionately wider in the left testis than in the right.

The cells of the tubules toward the periphery of the testes were, as far as spermatogenesis is concerned, inactive. Scarcely a mitotic figure was found. In the main these tubules had a single layer of spermatogonia and Sertoli cells with few, if any, spermatocytes. The spermatogonia were somewhat longer and narrower than the spermatogonia in tubules having one or more generations of spermatocytes. The more centrally located tubules were different. Usually in addition to the basal layer of spermatogonia there were one or two layers of spermatocytes. These spermatogonia more nearly approached the appearance of the spermatogonia of normal testes except for the fact that multiplication divisions were scarce. Maturation divisions also were few.

That the abnormal structure of the testes had hindered their normal functions is unquestionable. That the impaired functions of the gonads had reacted on somatic development, especially on the development of the secondary sexual characters, seems quite probable. The effects were similar in many respects to those following gonadectomy. The bird had the appearance of a capon. What had happened seemed to be a case of physiological castration.

The question arises, as it does in any consideration of the relation of the male sex glands to secondary sexual characters, what part of the testis effects the development of these characters? Are there certain determinable parts of the glands which, acting as endocrine organs, secrete a substance which stimulates the growth and development of comb and wattles, and modifies more or less bodily development and psychic behavior? It would

seem so, since removal of the entire glands results in profound bodily changes.

To certain cells in the inter-tubular material have been attributed the function of acting as ductless glands the secretion of which stimulates development of the secondary sexual characters. The fact that ligation of the vas deferens in birds results in atrophy of the seminiferous tubules and in a retention of, or possibly an increase in the normal amount of interstitial material, while the normal sexual characters are retained (Massaglia, 1921)*, indicates that these interstitial glands function in controlling secondary sexual characters.

The case of the bird under consideration, however, differs from the experimental cases. The gonads of the abnormal bird showed marked degeneration of the convoluted tubules and an increase in inter-tubular material, a condition similar to those produced by the ligation experiments. Coincident with these histological abnormalities was lack of development of some of the secondary sexual characters, a condition just the opposite of those resulting from ligation of the vas deferens.

This would seem to indicate that the inter-tubular material was not responsible for the development of comb and wattles, but rather that the spermatogenic or Sertoli cells might have had some role in controlling the growth and development of some of the secondary sexual characters. Such an idea has been advanced by Loisel (1902).

Not only is the idea of the endocrine function of spermatogenic tissue suggested by the present case, but the fact that in most cases of birds in which the male is more brilliantly colored, the intensity of color is heightened during the mating season, at which time the spermatogenic tissue is more active. That some endocrine function may be attributed to other parts of the male reproductive gland is admittedly possible, but that the cells of the convoluted tubules may serve as glands is also likely. Further investigation of these tissues by improved cytological methods may aid greatly in solving this perplexing problem.

*No attempt has been made to present a list of references since a comprehensive bibliography is given in Lipschutz, 1924, "The Internal Secretions of the Sex Glands." Williams and Wilkins, Baltimore.

Abstract Department

The effect of lowering blood pressure on myocarditis caused by epinephrine hydrochloride and caffeine in the rabbit. Barksdale (E. H.), Arch. Path. & Lab. Med. (Chicago), 1927, **3**, 658-660.

Lesions of the myocardium had been previously observed following a single injection of epinephrine hydrochloride and caffeine. Barksdale in the experiments here reported undertook to determine the relation of the increase in blood pressure caused by the injection to the lesions found. He employed two methods for preventing the rise in blood pressure: (1) bleeding combined with the inhalation of amyl nitrite; and (2) the injection of sodium nitrite followed by inhalation of amyl nitrite. It was not found possible by either of these methods to prevent the increase in blood pressure, but both greatly hastened the return of the pressure to normal. Eighteen control animals lived as long as six to seven days after the injection of ephinephrine and caffeine and all showed the characteristic lesion in the wall of the left ventricle near the auriculo-ventricular groove. Twenty-five animals, in which an attempt was made to prevent increase in blood pressure, lived as long as six to seven days after the injection of the epinephrine, and only fifteen, or 60 per cent, showed the lesion in the wall of the left ventricle. It appears, therefore, that the diminution in the duration in the action of epinephrine and caffeine prevented the production of the myocardial lesions in 40 per cent of the animals used. Barksdale concludes that in all probability the mechanical effects of the high blood pressure induced by the injections of epinephrine and caffeine are essential factors in the production of the myocardial lesions which follow such injections.—J. P. S.

On carbohydrate metabolism of adrenalectomized rats. Cori (C. F.) & Cori (Gerty T.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1927, **24**, 539-541.

Rats which have survived adrenalectomy show a decreased blood sugar after twenty-four hours' fasting. This is due to a lack of reserve glycogen in the liver. Such rats form glycogen from glucose at a normal rate. It is suggested that a disturbance in the formation of glucose from protein due to lack of adrenin or cortical material occurs. Experiments on adrenalectomized rats and mice

show that the inhibition of glycogen formation in the liver which follows injection of insulin is not due to adrenin.—J. C. D.

Anatomy and histology of the interrenal bodies of man (Beitrag zur Anatomie und Histologie der Interrenalkörper des Menschen). Iwanoff (G.), Ztschr. f. Anat. u. Entwcklngsgesch. (Berl.), 1927, **82**, 368-387.

The study is based on 132 bodies from newborn to 70 years of age, several fetuses 18-25 cm. long and a couple of animals. The retroperitoneal space along the abdominal aorta contained from 1 to 5 adrenal bodies in 60 per cent of the cases. They were most numerous on the right side. They varied in size from a millet seed to .5 x 5 cm. and are elongated in shape. Transitional forms between accessory adrenals and true isolated paraganglia were found after the second year. When they are associated with a well developed connective tissue capsule they were frequently infiltrated with lymphoid elements, mostly small lymphocytes, in the form of ill defined islands. There is a description of a central vein which is looked upon as the avenue by which the incretion leaves the gland.—A. T. R.

Influence of different diets on the nucleo-plasma ratio in the cells of the suprarenals of rats (Messungen an den Nebennierenzellen der Ratte. Einfluss verschiedener Ernährung auf die Kernplasmarelation). Kolliner (Martha), Ztschr. f. Anat. u. Entwcklngsgesch. (Berl.), 1927, **82**, 1-21.

Ten rats weighing in the neighborhood of 100 grams each and 2 rats weighing 60 to 70 grams each were divided into six pairs, each pair consisting of a male and a female animal of approximately the same weight. Each pair was given a different diet for about three months. In general these diets caused a considerable increase in body weight except wheat alone where the body weight remained near or only slightly above the initial weight. The nucleo-plasma ratio of the cortical cells in a wheat and cod liver oil diet was small, while in a pure wheat diet this ratio was relatively large. In a diet of wheat and yeast many cells in the cortex (except in zona glomerulosa) had a small nucleo-plasma ratio. In a diet of wheat and 1% calcium the cells in the cortex and medulla had a relatively large ratio, except in the outer part of zona fasciculata where the ratio was smaller than the average. In a diet of wheat, cod liver oil and calcium there was in general a smaller ratio than with a wheat and calcium diet. With a wheat and lemon juice diet the ratio in zona fasciculata was below the average and in the medulla it was distinctly larger. However, the number of animals in each group is too small for trustworthy generalizations.

—A. T. R.

A report of two cases of adrenal insufficiency (Addison's disease). Medlar (E. M.), Am. J. Path. (Boston), 1927, **3**, 135.

On the basis of the pathological changes found in the adrenals, cases of Addison's disease may be divided into two groups: (a) the more common form in which there is extensive destruction of adrenal tissue by tuberculosis, tumor growth, etc.; and (b) a rarer form of essential or idiopathic adrenal insufficiency in which neither infection nor neoplasm plays any part. The two cases reported by Medlar belong in the latter group. Case 1, concerned a man 28 years of age who was ill for only one week, with weakness, pigmentation of the skin, vomiting, etc. The chief findings at autopsy were status thymico-lymphaticus and atrophy and fibrosis of the adrenals. The second case was that of a woman aged 29 years, who had had a progressive pigmentation of the skin for two years and otherwise ran a more typical course of Addison's disease. At autopsy there were found: marked atrophy and destruction of adrenal tissue associated with hyperplastic lymphoid tissue; old rheumatic endocarditis; old healed bilateral pulmonary tuberculosis; bronchopneumonia, and hyperplastic islands of Langerhans. Medlar is of the opinion that these two cases emphasize the association between status lymphaticus and hypofunction of the adrenals; he suggests that status lymphaticus is an expression of an attempt on the part of the body to correct a deranged metabolism brought about by a paucity of adrenal secretion.—J. P. S.

A case of adrenal adenoma. Merriam (J.) & Smith (L. W.), Boston M. & S. J., 1927, **197**, 135-137.

The tumor was successfully removed. The patient had no systemic disturbances.—J. C. D.

The organization of experimental adrenal cell emboli in the lungs. Simonds (J. P.), Am. J. Path. (Boston), 1927, **3**, 13.

Rabbits were injected intravenously with a rather coarse emulsion of dog adrenals. There are certain resemblances between the histologic tubercle and the nodules produced in the lungs of rabbits by the organization of the emboli produced by these injections. This peculiar type of reaction is believed to be due to the high content of lipoid substances, especially cholesterol, contained in the adrenal cells.—Author's Abst.

Influencing peripheral action of epinephrine by extracts of organs. Steppuhn (O.), & Sargin (K.), Arch. f. exper. Pathol. u. Pharmacol. (Leipz.), 1926, **112**, 1-16.

An experimental paper containing a cut of the apparatus used, 5 curves and 3 tables of the essential observations. In spite of

much work the relation of the endocrine glands to the origin and course of labor in childbirth has not been solved. It has been observed that extract of the placenta has increased the uterine contracting power of adrenaline. An increased amount of adrenaline was found in the blood of gravid animals. The rôle of the placenta in childbirth may be greater than previously assumed. Using the isolated rabbit ear method of Krawkoff, these authors found that placenta extract, 1:500, caused a diminution of 70% in the number of drops flowing through the ear. Various other extracts gave similar results. With the guinea pig's uterus they observed contractions three or four times greater when placenta extract plus hypophysis extract was added than when hypophysis extract alone was used.—E. L.

Transplantation and individuality differential in strains of inbred rats. Loeb (L.) & King (Helen D.), Am. J. Path. (Boston), 1927, **3**, 143.

The results of homoio-, syngenesio- and auto-transplantation of thyroid, parathyroid, etc., in non-inbred rats were compared with those obtained in rats that were the product of long continued inbreeding by means of successive brother and sister matings. The data obtained from these experiments indicate that in contrast to the results obtained in inbred guinea pigs, where inbreeding led to a marked decrease in the intensity of the reaction and where the individuality differentials became very similar (although not yet identical through inbreeding), in the rat successive brother and sister matings, continued through many generations, do not lead to a marked increase in similarity of the individual differentials in the inbred animals.—J. P. S.

Syngenesiotransplantation in the guinea pig. Loeb (L.), Am. J. Path. (Boston), 1927, **3**, 29.

Loeb studied transplants of thyroid and parathyroid in guinea pigs. Syngenesio-reactions in this animal have a position intermediate in character between homoio- and auto-reactions. This intermediate character is due to the variations in individual reactions which approach auto-reactions on the one hand, and homoio-reactions on the other hand, as well as to a real intermediate syngenesio-reaction. The typical syngenesio-reaction resembles the auto-reaction as far as the behavior of the connective tissue and vessels is concerned. It differs from the auto-reaction in as much as subsequently lymphocytic masses invade the transplant. Brother to brother transplantations resemble autotransplantation to a higher degree than parent to children or the reciprocal transplantations. The grade of transplantations from parent to offspring does not seem to be significantly higher than the grade for the reciprocal

transplantation. Transplantations between grandparents and grandchildren have average higher grades similar to those of transplantations between parents and children. Relationship or dissimilarity (race differences) between the two parents seems to influence the intensity of reactions in the exchange of tissues between the various members of families.—J. P. S.

Syngenesiotransplantation in the rat. Loeb (L.), Am. J. Path. (Boston), 1927, **3**, 45.

Loeb transplanted thyroid, parathyroids and parts of other organs into rats. Syngenesiotransplantation in the rat shows an intensity of reaction which is intermediate between the reactions in auto- and homoio-transplantations. In both guinea pig and rat the average of individuality differentials of donor and host shows the smallest discrepancy in brother to brother transplantations; it is greatest in parent to children or children to parent transplantation. In general the reactions against syngenesiotransplantations in the rat are less severe than those in the corresponding syngenesiotransplants in the guinea pig. This condition is probably due to a greater homogeneity in the genetic composition of the rats than of the guinea pigs used by Loeb. The reactions against pieces of different organs derived from the same donor are relatively of the same strength because of the identity of the individuality differentials, although absolutely the reactions differ. The differences are due to secondary factors. On the basis of these secondary factors we may distinguish: (a) organs like the thyroid and parathyroid (in which variations in intensity of lymphocytic and connective tissue reactions cause the main differences in the fate of transplants); (b) organs like the ovary (in which, while the lympocytic reaction occurs, it is usually not very pronounced, but in which under the influence of very severe homoio-toxins only the more resistant component parts of the organ survive); (c) less resistant tissue like bone marrow, striated muscle tissue and to some extent also non-striated muscle tissue (the latter tissue survives or regenerates completely after transplantation for a longer period only in the absence of the more severe homoio-toxinism) and (d) very resistant tissues like cartilage and perichondrium.—J. P. S.

Significance of pseudoepiphyses in endocrinology (Über die Pseudoepiphysen und deren Bedeutung in der Endocrinologie). Rochlin (D. G.), Ztschr. f. Anat. u. Entwcklngsgesch. (Berl.), 1927, **82**, 354-367.

As a rule there is no epiphyseal ossification center on the distal end of the phalanges, first metacarpal and first metatarsal bones or on the proximal end of the second, third, fourth and fifth metacarpal and metatarsal bones. A more or less independent ossifica-

tion center in any of the above locations gives origin to what is termed a pseudoepiphysis. Pseudoepiphyses are more frequent in infantile retarded development and apparently where the endocrine disturbance is pluriglandular. Hypothyroidism seems to play a large rôle. Usually there is also hypogenitalism, but the sex glands are not considered to be a cause of the pseudoepiphyses. A pseudoepiphysis is especially frequent on the middle phalanx of the fifth finger. Bones with a pseudoepiphysis are usually too short. Pseudoepiphyses were not encountered in cases of excessive growth of bones in length nor in cases of accelerated differentiation as, e.g., in Basedow's disease and pubertas praecox. The report is based on 40 original cases with pseudoepiphysis, 32 of which were especially selected. The anomaly was present in 5.2% of children from 2 months to 10 years of age.—A. T. R.

Cyclic changes in the ovary of the mole (Untersuchungen über das Ovarium von Talpa europaea mit besonderer Berücksichtigung seiner cyclischen Veränderungen). Altmann (F.), Ztschr. f. Anat. u. Entwcklngsgesch. (Berl.), 1927, **82**, 482-569.

Serial sections of the ovaries of 98 specimens, representing every month of the year, were analyzed by projecting them on paper at various magnifications and then weighing the paper representing the various constituents. Thirty-one of these animals were killed in March during the active sexual period and pregnancy. The interstitial cells decrease greatly during the active sexual period in the spring. This and the other elements in the ovary are discussed from the standpoint of their probable rôle in the sex cycle—A. T. R.

Action of follicular fluid on uterine contractility. Brouha (L.) & Simonnet (H.), Compt. rend. Soc. de biol. (Par.), 1927, **96**, (2), 96-97.

When the resting uterus of the rat in vitro shows only small contractions, addition of fresh liquor folliculi (or extracts of it) augments the amplitude of contractions. With the guinea-pig uterus tonus is increased without inducing contractions. The question is raised as to whether the follicular hormone acts directly upon the uterine musculature in vitro.—E. A.

Female sex hormone, Menformon (Ueber weibliches Sexuahormon im bes. das Menoformon). Laqueur (E.), Klin Wchnschr. (Berl.), 1927, **6** (9), 390-396.

A summary of the author's contributions to this subject with references to other recent work. Laqueur's product, Menformon, is a clear water soluble preparation standardized at 10 mouse units

per mgm. It is readily dialysable, quite thermostabile and resistant to action of acids and alkalis. The principal animal reactions are: in females, growth of the vagina and uterus; in males, inhibition of growth of the testes and external genital organs. It induces an increase in rate of metabolism and has no harmful circulatory effects. Its therapeutic possibilities are discussed. The author considers the question unsettled as to whether one or several hormones are involved in female sex phenomena.—E. A.

A qualitative indicator for the testis hormone. Moore (C. R.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1927, **24**, 847-848.

In guinea pigs after removal of one testis the spermatozoa in the epididymis of the operated side retain motility for 60 days. If both testes are removed, i.e., all source of testicular hormone eliminated, motility is lost in about one-half this time.

Studies on the internal secretion of the ovary. IV. The significance of the occurrence of oestrin in the placenta. Parkes (A. S.) & Bellerby (C. W.), J. Physiol. (Lond.), 1927, **62**, 385-396.

Extracts were made (details given in original paper) from placentae of seven pregnant sheep, ten cows and thirty-six humans, also from amniotic fluid from sheep and cows, from whole sheep fetuses and from pregnant uteri of sheep and cow. In all the three latter sources small amounts of oestrus-producing substance were found. The placental preparations gave comparatively large yields. Where separate extractions were made from maternal and fetal placentae, oestrin was fairly equally divided between the two. The authors believe their results suggest that oestrin in the placenta is due to withdrawal from maternal circulation and not to elaboration by the placenta itself.—C. I. R.

Catabolism of sex glands in a case of pseudohermaphroditism (Über den Geschlechtsdrüsen abbau bei einem Fall von Pseudohermaphroditismus). Rinck (H.), Ztschr. f. Konstit. (Berl.), 1927, **13**, 209-211.

The description is given of a three-and-a-half-year-old girl with an abnormally long clitoris without an opening and having the appearance of a glans penis with the foreskin pulled back. The labia majora had the appearance of a scrotum. The internal organs were apparently those of a normal female and in some respects she acted like a girl (played with dolls, e. g.), but was rough and ill-mannered like a boy. Physical measurements are given. Abderhalden's serological catabolic test was made 8 times by the Hirsch interferometric method and showed that the testicular reaction was stronger than the ovarian, while the reverse is true of normal girls.—A. T. R.

Influence of insulin upon the mammalian heart. Visscher (M. B.) & Müller (E. A.), J. Physiol. (Lond.), 1927, **62**, 341-348.

An investigation of effects of insulin on (a) the mechanical condition of the mammalian heart in the heart-lung preparation and in the whole animal and (b) oxygen consumption of the heart. Three brands of insulin were used, all of which, in the heart-lung preparation, decreased the size of the ventricles. There was no change in inflow or output. Two brands (B. D. H. and Boots) did not alter the rate. The third preparation (Wellcome) increased the heart rate. These effects held for both normal and diabetic dogs (depancreatized). A second application was ineffective, which fact the authors conclude indicates that the action is specific and not due to alkaline buffers, salt water nor small amounts of adrenalin. In intact anaesthetized dogs, both normal and diabetic, insulin caused a sustained rise in arterial pressure without any change in ventricular volume. In the heart-lung preparation, insulin did not cause any increase in the rate of oxidation of food stuffs in the heart. Oxygen usage following insulin is determined by the diastolic ventricular volume and the heart rate.—C. I. R.

Some problems of the menstrual function with observations on the relation of the Graafian follicle and corpus luteum to pathological uterine hemorrhage. Whitehouse (B.), Edinburgh M. J., 1927, **4**, 139-155. (Transactions Edinburgh Obstetrical Society Session 86.)

In a number of the author's cases destruction of the corpus luteum has brought on rapid degeneration of the uterine decidua with typical menstruation. This and other facts from the literature indicate that in the human uterus there are two cycles. The one is a typical oestrous cycle with a resting period between each ovulation. The other is dependent on the period following ovulation which corresponds not only to a resting period but to the period of pseudo-pregnancy found in certain animals. Hemorrhage of menstruation is due to the uterine congestion of the oestrous combined with the necrosis of the endometrium due to the "abortion" of the pseudo pregnancy. No references to the literature are included.
—J. C. D.

Acromicria (Über Akromikrie [Brugsch]). Ballmann (E.), Ztschr. f. Konstit. (Berl.), 1927, **13**, 241-251.

The patient, now 38 years old, was treated when 12 years of age for pain in the hands and feet which were swollen and stiff most of the time and often felt numb. He had numerous attacks of dizziness and finished school 2 years after the average age. The

pain in the hands and feet persisted and varicose veins and ulcers of the legs developed. The ears were small as if a part had been cut off. Antisyphilitic treatment had no effect. When the patient was first seen by Ballman in 1922 his fingers were atrophic with cyanotic and shiny skin, the ears were contracted, and the vision was failing. The Wassermann test was negative. He had never had sexual desires. At present he weighs 60 kilograms and has atrophy of both bones and soft parts of fingers and toes. The fingers are pointed and cyanotic when allowed to hang down. The toes are in a hammer position. The sella turcica is decidedly small. There is abundant hair on the head and body. The blood showed 6½ million erythrocytes, 10,300 leukocytes, 110% hemoglobin, and 10 hours sedimentation time. There is no diabetes insipidus in this case as there was in the case described by Brugsch. Congenital syphilis is indicated by virtue of having a chondrodystrophic dwarf sister, although the Wassermann reaction was generally negative. While acromicria, or dystrophia osteogenitalis, has been regarded as the opposite of acromegaly, and due to hypophyseal disturbance setting in after growth has ceased, this patient has had the disease from childhood; hence the author thinks Biedl's theory more probable, namely, that it is due to a different kind of cell in the hypophysis being affected. He regards acromicria as probably a hypofunction of the eosinophilic cells of the anterior lobe of the hypophysis. He emphasizes the necessity of making a distinction between the primary signs of disease of the anterior lobe and those which are due to involvement of other parts of the hypophysis or other interrelated endocrine glands.—A. T. R.

The relation of the hypophysis to diabetes mellitus. Colwell (A. R.), Medicine (Detroit), 1927, **6**, 1-39.

The author gives an extensive review of the literature. He reports one case in which diabetes developed in the third year of acromegaly, and in which the patient promptly responded to insulin. Within a year his tolerance for carbohydrates was improved significantly, a point which the author stresses in his review of the literature. While diabetes which accompanies acromegaly resembles ordinary diabetes mellitus in nearly all respects, it differs from it in the fact that it is capable of undergoing spontaneous, temporary or permanent recovery, which fact the author considers as highly significant. He concludes that the rôle of the hypophysis in carbohydrate metabolism is not definable with certainty at the present time but that it is probably without significance in this field as a gland of internal secretion. Important nerve centers or pathways are situated in or near it which are possibly concerned in the control of the metabolism of carbohydrates and that it is

not impossible that these centers or tracts are involved in the control of insulin secretion.—H. J. J.

A quantitative study of the hypophysis of the human anencephalic fetus. Covell (W. P.), Am. J. Path. (Boston), 1927, **3**, 17.

Covell found hypophysis tissue in each of the 32 human anencephalic fetuses examined. The weight was very variable, and when corrected for vascularity it was usually less than the corrected weight of the hypophysis of normal fetuses of the same age. The pars nervosa was lacking in the majority of cases; when present at all its relative and absolute volumes were considerably less than those of the normal. The pars intermedia was variable both in occurrence and volume; it might be present in a gland in which the pars nervosa was absent. The pars anterior comprises most of the gland volume and apparently the total gland volume in many instances. The average relative volume of blood present in the anterior lobe is about 39% of the volume of that lobe.—J. P. S.

The effects of feeding anterior lobe pituitary extract to children. Gardiner-Hill (H.) & Smith (J. F.), Lancet (Lond.), 1926, **211** (5370), 219-222.

The authors report in this paper the results of administering anterior lobe pituitary extract (Armour) to under-developed children. Three types of cases were included: first, children with infantilism and defective growth; secondly, older female children with minor degrees of this condition accompanied by disturbances of menstruation; and thirdly, children with obesity of the apparently endogenous type. Two representative cases of each type were studied ranging in age from 9 to 19 years. A common metabolic disturbance in the form of a lowered sugar tolerance occurred in the first two groups before treatment. There was a slightly increased tolerance in the third. Bone development was definitely delayed as shown by X-Ray. The sella turcica was essentially normal in size in all cases. The effect of giving from 3 to 15 grains of extract daily was to produce a demonstrable increase in the sugar tolerance in every instance. The cases showing infantilism were found to gain in both height and weight at a rate greatly exceeding the normal. Menstruation became regular after treatment in one case of secondary amenorrhea, but was not affected in another in whom it had never occurred even at the age of 19 years. The obesity was unaffected in those cases in which it was a factor.—I. M.

Influence of pituitrin on diuresis variously induced. Knowlton (F. P.), Curtis (A. N.) & Silverman (A. C.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1927, **24**, 865-869.

The authors conclude that when diuresis is induced in anesthetized rabbits by the method of continuous intravenous injection pituitrin acts to augment such diuresis. The effects are similar with various diuretics and with varying dosage and administration of the pituitrin. A table of results is included.

Dystrophia adiposogenitalis in three brothers (Familiares Auftreten von Dystrophia adiposogenitalis bei drei Brüdern). Rahlfs (S), Ztschr. f. Konstit. (Berl.), 1926, **12**, 758-778.

The author describes three sons of a syphilitic father. There were no signs of tumors of the hypophysis in any of them. Two showed dwarfism, which is taken to indicate some involvement of anterior lobe of the hypophysis. Intelligence was normal and the Wassermann negative in all.—A. T. R.

Preferential utilization of carbohydrate in diabetes. Campbell (W. R.) & Markowitz (J.), J. Clin. Investigation (Balt.), 1927, **4**, 37-52.

The authors studied the question of preferential utilization of carbohydrates (levulose, insulin, dihydroxyacetone, glycerine) in completely depancreatized dogs which were given a definite number of units of insulin before and throughout the test. Their results published in tables show no evidence that greater quantities can be utilized by the diabetic organism than of glucose itself, which fact suggests that these substances must pass through a glucose phase in their metabolism and therefore do not undergo any preferential utilization as compared with other carbohydrates.—H. J. J.

Synthalin—Substitute for insulin for oral medication (Über synthetisch dargestelle Körper mit insulinartiger Wirkung auf den normalin und diabetischen Organismus). Frank (E.), Nothmann (M.) & Wagner (A.), Klin. Wchnschr. (Berl.), 1926, **5**, 2100-2107; Abst., Am. J. Med. Sci., **174**, 278-279.

The authors report a synthesised product, called synthalin, which is an alkaline guanidin derivative. It lowers blood sugar and can be taken by mouth. When given to rabbits which have been starved 24 hours, in doses of 3 to 4 mgm. per kgm., it reduces the blood sugar to the point of convulsions. These are immediately relieved by the injection of glucose. In depancreatized dogs synthalin given in sufficient quantities causes a cessation of the glycosuria and lowers the blood sugar to the borderland of convulsions. In human diabetics it may cause the disappearance of 30 to 40 gm. of glucose from the daily output of urine. Its action is more delayed than that of insulin, being retarded sometimes as long as 24 hours, but it continues over a longer period of

time. It may produce, even in therapeutic dosage, a loss of appetite, rapid peristalsis, nausea and possibly vomiting. The authors recommend, therefore, commencing with small doses and working gradually up to what is necessary. When it is desired to change from the insulin treatment to the newer synthalin it is recommended also that both drugs be given at the same time, and that the amounts of synthalin be slowly increased while at the same time one lowers the dosage of insulin correspondingly. They conclude that this preparation lowers the sugar in the urine, 1 mgm. taking care of 1.1 to 1.2 gm. of sugar: that the blood sugar is brought down below the point where glycosuria occurs; that acidosis is relieved; that other symptoms of diabetes, such as polyuria and polydipsia, are removed. It is found useful in cases with temporary infection or those that are "insulin refractory": in diabetics with surgical infections, such as gangrene, furunculosis and phlegmons, it may be used in place of insulin. The contraindications for the use of synthalin are severe acidosis and diabetic coma, when the more powerful and more rapid action of insulin should be depended on until the emergency is past.

Rôle of vitamins and insulin in nutrition. Funk (C.), Paris méd., 1927, **61**, 389-392.

A history of the vitamins and a review of the author's recent work on insulin is given in this paper. A new classification of the vitamins is also suggested. The vitamins proper are substances containing nitrogen and are very sensitive to alkali. They are named as follows: B—anti-neuritis, C—anti-scorbutic, D for the growth of micro-organisms and P for the prevention of pellagra. The vitasterols or vitasterines are characterized by not containing nitrogen and being very sensitive to oxidation. Vitasterol A is anti-xerophthalmic, E is anti-rachitic and F is necessary for reproduction. Substance A, which represents the pancreatic hormone, causes a lowering of the blood sugar in a diabetic, but in a normal individual there is no effect. The reason for this action is that substance C, or co-insulin, is necessary for the activation of A. In the normal being, A and C are present in proportional amounts. Therefore the introduction of an excess of A will not decrease the blood sugar because it is not activated. In a diabetic there is an excess of C, and A upon its introduction is promptly activated and then reduces the blood sugar. Substance B, an anti-insulin, has also been isolated from the pancreas. This substance will cause hyperglycemia and pancreatic disturbances.—E. L.

Diabetes refractory to insulin. Häusler (H.) & Högler (F.), Klin. Wchnschr. (Berl.), 1927, **6**, 541-543.

Experiments were conducted with the blood corpuscles and blood plasma of normal, diabetic and insulin refractory diabetic persons. From their work these investigators came to the conclusions that the blood plasma of the insulin refractory person does not have the power to bind glucose, but that the glucose binding is done by the blood corpuscles. This glucose binding power can be removed by repeated washings of the corpuscles. —E. L.

A clinical study of substance A isolated from insulin. Landsberg (M.), Progrès méd. (Par.), 1927, **54**, 242-245.

A preliminary communication reports the results with substance A on the blood sugar of both normal and diabetic persons. When 1.2 mgm. (equivalent to 20 units of insulin) was injected into a series of ten diabetics there was a fall in the blood sugar varying from 41 to 109 mgm. The oral administration was ineffective. When normal individuals received the same dose there was an increase of 4-35 mgm. in the blood sugar in five cases and a decrease of 4 mgm. in one case.—E. L.

Depancreatized dogs kept alive several months with insulin administered by stomach tube. Murlin (J. R.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1927, **24**, 549-550.

Insulin in ox-blood serum was used. Its effects on respiratory metabolism were immediate, and persisted for twenty-four hours or more. Daily doses kept depancreatized dogs alive for from six weeks to four months.—J. C. D.

Studies on the islands of Langerhans in human pancreas. I. The relation of the islands to the surrounding structures. Otani (S.), Am. J. Path. (Boston), 1927, **3**, 1.

This paper is a contribution, copiously illustrated with photomicrographs, to the still disputed question of the relation of the islands of Langerhans to the surrounding tissue of the pancreas. Otani's study is based upon the examination of the pancreas in each of 46 cases ranging in age from 3 days to 76 years. Silver impregnation was the staining method used. Three types of islands were recognized in the normal pancreas: (a) islands connected with surrounding acini, found in every case; (b) islands connected with interlobular and intralobular ducts; and (c) islands strictly separated from the surrounding structures. The islands have no

fibrous capsule of their own, but a more or less complete separation is produced by the basement membrane of the acini or ducts or by the interlobular connective tissue. There are wide variations in size, shape and relation of the islands to the surrounding pancreatic structures. Such differences are present not only in the same organ but even in the same sections. Therefore it is improper to speak of one regular type of island of Langerhans in respect to this relation.—J. P. S.

Studies on the islands of Langerhans in the human pancreas. II. Significance of variation in structure. Otani (S.), Am. J. Path. (Boston), 1927, **3**, 123.

This paper is concerned with the significance of the varying types of islands of Langerhans described by Otani in a previous paper. The process of hypertrophy of these islands in adult pancreas is chiefly due to transformation and hyperplasia of acinar and centroacinar cells, the hyperplasia of the island cells, proper, being relatively insignificant. The acinar cells are able to change into island cells; whether the reverse change can take place is uncertain. Direct contact between islands and acini indicates a genetic relation. One type of island connected with ducts is interpreted as a remnant in the postembryonal pancreas or as resulting from the transformation from acinus to island cells, while the other type has a definite relation to the new formation of islands in the adult pancreas. The fact that islands entirely separated from the rest of the pancreatic tissue do exist under normal pathologic conditions may be regarded as morphologic evidence of an internal secretory activity of the islands. They cannot be accepted, however, as constituting an organ sui generis, since normally most of the islands are connected with acini which are capable of changing into island cells. The new formation of islands in adult pancreas may occur by transformation and hyperplasia of the acinar, centroacinar or duct cells. The article is copiously illustrated with photomicrographs.—J. P. S.

Diabetes complicating acromegaly and pituitrin-insulin antagonism. Wemyss (H. L.), Edinburgh M. J., 1927, **34**, 343-346.

This is a case report. Insulin injections lowered the blood sugar but when insulin and pituitrin were used the sugar level was not reduced.—J. C. D.

Growth of the thorax, heart, lungs and thymus in swine (Über das Wachstum des Brustkorbes und der Brustorgane (Herz, Lunge,

Thymus) während der Entwicklung beim Schweine). Lenkeit (W.), Ztschr. f. Anat. u. Entwcklngsgesch. (Berl.), 1927, **82**, 603-642.

One hundred and twenty-one animals from the 4th to the 16th week were investigated biometrically. The report is largely of morphological interest.—A. T. R.

Iodin as a therapeutic aid to surgery in primary hyperthyroidism. Clute (H. M.), & Mason (R. L.), Boston M. & S. J., 1927, **197**, 247-254.

The authors conclude from a study of their cases: that iodin is the important factor, for they got as good pre-operative results with hydriodic acid saturated with iodin as with Lugol's solution; that an excess of iodin is better than continued smaller doses; that iodin therapy should continue three months after operation; that some recurrences may be controlled with iodin, though as a rule further excision is indicated; that iodin is not a cure for exophthalmic goitre; and that iodin may be cautiously tried in pre-operative treatment of patients having multiple adenomatous goitres with hyperthyroidism.—J. C. D.

Management of the hypothyroid patient. Higgins (W. H.), South. M. J. (Birmingham), 1927, **20**, 779-782.

The author emphasizes the observation of the basal metabolism, as indicating the effectiveness of the treatment and the need of correcting co-existing pathological conditions.

Toxic goiter. McClure (R. D.), & McGraw (A. B.), Ann. Clin. Med. (Balt.), 1927, **5**, 626-634.

The authors have drawn upon their experience with a series of 211 cases, operated upon in 1925, to assemble their current views on the management of patients suffering from so-called toxic goiter. They bring out statistically that the degree of toxicity varies much more strikingly with the type of goiter encountered than with the age at which the goiter or its toxic symptoms made their appearance. They advocate the closest possible co-operation between surgeon and internist during the entire time the patient is under observation. They feel that adenomatous goiters should be excised, whether toxic or not, as a safeguard against future trouble. They discuss the relation of such associated complications as myocarditis, with or without auricular fibrillation, and diabetes mellitus to the

operability of cases with hyperthyroidism and reach the conclusion that these two complications are rarely if ever a barrier to successful operation if conducted with sufficient caution. In outlining pre-operative measures, they stress complete rest in bed, the use of iodine (Lugol's solution) in moderate doses, high fluid and food intake, and the use of mild sedatives, such as luminal. Post-operative treatment is likewise outlined emphasizing the maintenance of a large fluid and sugar intake immediately after operation by means of hypodermoclysis, proctoclysis, and intravenuous medication if necessary. They stress the necessity of frequent follow-up visits during the first six months after operation in order to curtail the patients' activities and to detect promptly any signs of persistent or recurrent hyperthyroidism.—Authors' Abst.

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